THE PREVALENCE, CORRELATES, EFFECTS AND DETECTION OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN AN URBAN POPULATION

THERESA A McDONAGH

Submitted for the degree of Doctor of Medicine

UNIVERSITY OF EDINBURGH

1998

CONTENTS

ACKNOWLEDGEMENTS

The work presented in this thesis was carried out in Professor HJ Dargie's Research Unit in the Department of Cardiology at the Western Infirmary, Glasgow. It was funded, chiefly, by a grant from the Scottish Office Home and Health Department. I have drawn upon the skills of many, I cannot mention them all, but I wish to cite those who have been most involved.

As it was a collaboration with the Scottish MONICA Project, I wish to thank Dr Caroline Morrison for her tireless efforts in making the MONICA Population available for screening again and her endeavours to ensure an optimal response rate. I would also like to acknowledge her kindness to me personally during the painstaking hours of echo analysis. The expert skills of others at the MONICA project were also invaluable: Wilma Leslie, Aileen Urie and Mary Mitchell for the exercise test coding.

The help of my "screening team" has left an enormous impression on me. The echocardiograms were in the main carried out by Esther Rooney, to whom I am much indebted. I wish to thank Susan Davison for her expertise in performing and coding the exercise tests and Wendy Linden for "manning" the nursing station.

The natriuretic peptide measurements were performed in the lab of Dr Ian Morton and funded by Merck Sharpe and Dohme.

All the data collected in this study was entered at the Robertson Centre for Biostatistics at the University of Glasgow. I wish to thank Audrey Lawrence

for her assistance in data management and Professor Ian Ford for his statistical advice.

I also wish to extend by gratitude to Francois Cambien and his staff at French Inserm for carrying out the ACE genotyping and also to Sandy Cook at the RHSC for extracting the DNA.

I must also acknowledge all the randomly sampled subjects from North Glasgow who attended the study and endured the rigours of an echocardiogram, exercise test and blood sample with the characteristic far-sightedness and cheerfulness of Glaswegians. It my earnest hope that any use of this data for provision of health care in the future will be of benefit to them.

I would like to express my thanks to my colleagues John Byrne and John McMurray for screening a session per week in the early stages of this project. I also acknowledge the help of John McMurray with some of the manuscripts which this work generated. I am grateful to Stephen Robb for undertaking my CRI committments while I analysed the echocardiograms. I am also indebted to Malcolm Metcalfe who critically read the first draft of this thesis.

Very few people have the privilege of undertaking research in such an excellent environment as I did, which leaves me to thank Professor Henry Dargie for providing me with the opportunity. I also commend him for his interminable patience with me and for his inexhaustible optimism and enthusiasm, which has often kept me going.

Above all I would like to thank my parents. This work, quite simply, would not have been possible without them.

ABSTRACT

The prevalence of chronic heart failure (CHF) in most epidemiological studies has been determined by using clinical criteria.

In this thesis, in contrast, left ventricular systolic function was assessed objectively by echocardiography in a cross-sectional survey of 2000 men and women aged 25-74, randomly sampled from a geographical area. Left ventricular ejection fraction (LVEF) was measured using the Biplane Simpson's Rule Method. Its aims were to document the prevalence of both symptomatic and asymptomatic left ventricular systolic dysfunction; ascertain the correlates of left ventricular systolic dysfunction; assess its effects on effort capacity; determine the usefulness of the natriuretic peptides in detecting systolic dysfunction; and to explore the possibility of a genetic component to left ventricular systolic dysfunction by examining the relationship between left ventricular systolic dysfunction and the angiotensin-converting enzyme insertion/deletion polymorphism (ACE I/D).

In the 1640 subjects who attended (83%), the mean left ventricular ejection fraction was 47.3%. The prevalence of 'definite' left ventricular systolic dysfunction (a LVEF≤30%) was 2.9%: it was 0.7% in men aged 35-44 years and 6.4% in men >65 years being also higher in men (4%) than women (2%). One point five percent (1.5%) had symptomatic left ventricular systolic dysfunction and 1.4% asymptomatic left ventricular systolic dysfunction.

In those with left ventricular systolic dysfunction, 83% had evidence of ischaemic heart disease (IHD), in contrast to 21% of those without left

ventricular systolic dysfunction ($p<0.001$). Hypertension was more common in those with an abnormal ejection fraction (60% compared to 22%), $p<0.001$) but hypertension unaccompanied by IHD was not significantly more common in those with left ventricular systolic dysfunction.

Left systolic ventricular dysfunction was associated with a significant reduction in exercise duration. In subjects in whom this was asymptomatic there was a trend towards decreased effort capacity.

Plasma concentrations of the natriuretic peptides were significantly higher in those with left ventricular systolic dysfunction (the median concentration (interquartile range) of N-ANP was 2.8 [1.8,4.6] ng/ml and BNP; 24 [18,33] pg/ml) than in those without (N-ANP; 1.3[0.9,1.8] ng/ml and BNP; 7.7pg/ml[3.4,13], $p<0.001$). The area under the Receiver Operator Characteristic Curves (SD) was greater using BNP; 0.88 (0.03) for all, 0.841 (0.03) in those with IHD, 0.86(0.03) for subjects ≥55 years and 0.84 (0.04) for those ≥55 years with IHD. The same areas under the curve for N-ANP were 0.75(0.05), 0.71(0.05), 0.72 (0.05) and 0.70 (0.06), respectively. A BNP concentration of ≥17.9pg/ml gave a sensitivity of 77% (specificity 87%) for detecting left ventricular systolic dysfunction in all subjects, improving to 92% (specificity 72%) when the analysis was restricted to individuals ≥ 55 with IHD.

The DD genotype of the ACE I/D polymorphism was significantly more common in subjects with electrocardiographic evidence of myocardial infarction (MI) or major ischaemia. (Using II as a reference, the odds ratios normal versus major ischaemia or MI were: DD 1.53, ID 1.18:$p=0.03$ for

trend). In older patients (≥51 yr.) with an ECG MI or major abnormality, LVEF was higher in those with the DD genotype (LVEF%: DD 44.6, ID 42.9, II 40;$p<0.02$). LVEF was also greater in older patients with a systolic blood pressure (SBP) > than the median value (LVEF%: DD 47.5, ID 45.8, II 44.6; $p=0.012$).

This work has shown that left ventricular systolic dysfunction is at least as twice as common than previous studies based on clinical criteria of CHF would suggest; about half is asymptomatic. Only 18% of subjects with definite left ventricular systolic dysfunction were taking an ACE inhibitor. Its main risk factors are IHD and hypertension in the presence of IHD; screening such high risk groups for left ventricular systolic dysfunction is worthy of consideration. Using a test such as BNP and targetting its use to individuals at high risk would lead to the identification of many more patients with left ventricular systolic dysfunction and, therefore, to the uptake of effective treatment. It would also lead to a more cost effective use of further investigation.

This thesis also provides a mechanistic insight into the development of left ventricular systolic dysfunction by suggesting that while the DD genotype confers a higher risk of MI, it is associated with better preservation of LV function post MI, possibly by enabling more adequate compensatory hypertrophy. The ACE gene I/D polymorphism may, therefore, have a bi-directional importance in determining both the risk of MI and post MI LV systolic dysfunction.

FORMAL DECLARATION

I declare that I have written this dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observations and that, except as acknowledged in this thesis, the data were collected and interpreted by me. This thesis has not been submitted for any other degree.

THERESA A McDONAGH

FORMAL DECLARATION

I declare that I have written this dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observations and that, except as acknowledged in this thesis, the data were collected and interpreted by me. This thesis has not been submitted for any other degree.

THERESA A McDONAGH

Chapter 1

GENERAL INTRODUCTION

1.1 Chronic Heart Failure and Left Ventricular Systolic Dysfunction

1.1.1 The Syndrome of Heart Failure

Heart failure has been defined, in pathophysiological language, as a "state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues or, to do so, only from an elevated filling pressure" (Braunwald, 1997). Whilst this is useful for the physiologist, the clinician requires a more pragmatic approach and it is at this point that problems with definition begin to emerge.

The difficulty in defining heart failure, clinically, stems from the fact that heart failure is not a diagnosis, per se, but a clinical syndrome consisting of a constellation of symptoms and signs attributable, ultimately, to cardiac dysfunction. As such, it represents the final common pathway for most serious forms of heart disease (Lenfant, 1994).

Contained within the above definition is a wide spectrum of pathophysiological states varying from those caused by rapid impairment of pump function eg. massive myocardial infarction, tachy or brady arrhythmias to the progressive and gradual impairment of myocardial function observed in a patient whose heart is subjected to pressure or volume overload for a prolonged period.

1.1.2 Chronic Heart Failure

This is the most common manifestation of heart failure and has largely replaced terms like "congestive cardiac failure", "left heart failure", "left ventricular failure" and "low output failure" as it describes more accurately the

persistent nature of the condition. Chronic heart failure (CHF) often follows an undulating course, being punctuated by episodes of decompensation. It occurs when one or more of several distinct pathologies which can also cause acute heart failure develop gradually or when the patient survives the initial insult and a number of adaptive mechanisms become operational allowing the patient to survive but with depressed cardiac function either at rest or on effort.

1.1.3 Definition of Chronic Heart Failure

Ideally, chronic heart failure should be diagnosed when a patient has:

1 Symptoms of heart failure at rest or on effort, and

2 Objective evidence of cardiac dysfunction at rest.

A third element, that is, a response to treatment, with a diuretic, digoxin or angiotensin converting enzyme inhibitor, is also desirable, especially where the diagnosis is in doubt (Task Force on Heart Failure of the European Society of Cardiology, 1995).

A simpler or more precise definition of chronic heart failure, currently, is unavailable as there is no cut-off value of cardiac dysfunction, be that a change in a parameter of contraction, thickening, flow, pressure, dimension or volume that can be used, reliably, to identify subjects with heart failure. The diagnosis relies on good clinical judgement based on the history, physical examination and appropriate investigations.

1.1.4 Cardiac Dysfunction

Thus, an essential element in the diagnosis of heart failure is the presence of cardiac dysfunction of which there are many types. Valvular, endocardial,

pericardial, myocardial pathologies and some extracardiac abnormalities, are all capable of producing the end stage condition of dyspnoea, fatigue and fluid retention. The relative importance of the different structural components of the heart as causes of heart failure varies geographically with the prevalence of the important types of heart disease i.e. ischaemic, hypertensive, rheumatic, valvular, infective, congenital and cardiomyopathic.

1.1.5 Left Ventricular Dysfunction: Systolic and Diastolic

By far the most common cause of chronic heart failure in industrialised societies is left ventricular dysfunction (LVD) due to myocardial disease and in particular, left ventricular systolic dysfunction. Here, pump failure occurs as a consequence of failure of contraction of the left ventricle (LV), most often as a result of myocyte loss secondary to myocardial infarction.

Less commonly, chronic heart failure can result from failure of relaxation of the left ventricle leading to impaired filling. This diastolic dysfunction accounts for between 30-40% of all chronic heart failure, and becomes increasingly prevalent with advancing age. It is also encountered more frequently in those with pre-existing systemic hypertension (Dougherty et al. 1984,Soufer et al. 1985) as well as being the predominant variety of ventricular dysfunction in rarer conditions such as hypertrophic obstructive cardiomyopathy and amyloid. The natural history of diastolic dysfunction is not well studied. It is, however, thought to be associated with a better prognosis than systolic dysfunction (Nelson et al. 1975).

The picture is further complicated in those with left ventricular dysfunction, due to IHD when both systolic and diastolic dysfunction frequently co-exist,

the former due to loss of myocardium and the latter due to one or more of replacement fibrosis, hypertrophy of non-infarcted myocardium and possibly, myocardial ischaemia.

1.1.6 Left Ventricular Systolic Dysfunction

In most cases, chronic heart failure is now thought to lie at the end stage of a progressive deterioration in left ventricular function, which can remain asymptomatic for years. In other words, when heart failure is diagnosed on symptoms and signs, the end stage of the disease is being detected - where it can have a mortality, untreated, of up to 50% per annum (Swedberg et al. 1987). Thus, the full blown syndrome can be preceded by a long, latent phase, during which left ventricular damage is certainly present, but in which diagnosis on clinical grounds is impossible. This latent phase is commonly referred to as one of "asymptomatic left ventricular dysfunction".

1.1.7 From Asymptomatic Left Ventricular Systolic Dysfunction to Chronic Heart Failure.

In the majority of patients who develop CHF the sequence of events begins with a myocardial infarction. Although many patients develop transient left ventricular failure in the acute phase of myocardial infarction, most patients recover satisfactorily (Nicod et al, 1988) despite electrocardiographic and cardiac enzyme evidence of substantial myocardial damage, to be left with asymptomatic left ventricular systolic dysfunction. In this state symptoms and signs of heart failure are lacking but objective assessment of cardiac function either non invasively, by echocardiography or radionuclide ventriculography, or invasively, by angiocardiography reveal depressed left ventricular

contractility. The left ventricular ejection fraction is the most commonly used parameter of left ventricular systolic function as it is associated, independently with prognosis (Nelson et al. 1975). The cut-off value taken to indicate significant left ventricular systolic dysfunction varies with the method of measurement and between centres but is generally less than or equal to 35-40%.

The natural history of patients with left ventricular systolic dysfunction after myocardial infarction is not well documented. Some develop recurrent myocardial infarction which further compromises their left ventricular function often precipitating overt heart failure which may subsequently become chronic. Others, however, progress to the heart failure stage without further myocardial infarction. The heart undergoes a process of remodelling resulting in progressive loss of contractile function leading to symptomatic left ventricular systolic dysfunction (Mitchell et al. 1995). In these subjects, the initial infarct size is usually the dominant factor in their progression to overt heart failure (Moye et al. 1989). Other contributing risk factors are the neuroendocrine, vascular and renal responses that occur in individuals with left ventricular systolic dysfunction.

Although all appears to be well in subjects with asymptomatic left ventricular systolic dysfunction, there is evidence to suggest that compensatory neuroendocrine activation is already occurring, with increases in the plasma levels of noradrenaline (Francis et al. 1990) and natriuretic peptides (Lerman et al. 1993). In addition impairment of aerobic capacity on exercise has also

been demonstrated in those with subclinical left ventricular systolic dysfunction (LeJemtel et al. 1994).

1.1.8 Multisystem Dysfunction

Although the primary problem in chronic heart failure is cardiac, the clinical syndrome is characterised by secondary multi system dysfunction which ultimately leads to a terminal state of multi organ failure.

Returning to our physiological definition of heart failure, there is an important variable which contributes to the adequacy of oxygenation of the metabolising tissues and that is the blood pressure (Harris, 1987), of which the cardiac output is a major determinant. The reduction in cardiac output which occurs in left ventricular systolic dysfunction, activates a myriad of mechanisms which have evolved to maintain it and which, presumably, were designed to protect the organism from haemorrhage or the hypovolaemia of dehydration.

Among the major components of this so called compensatory response are the sympathetic and renin angiotensin systems. Thus, noradrenaline is released, resulting in an increased heart rate and vasoconstriction. Decreased renal perfusion causes increased production of the powerful vasoconstrictor Angiotensin II which causes sodium retention through the combined actions of aldosterone and increased renal sympathetic activity. Water retention is also enhanced by vasopressin production from the posterior pituitary (Francis et al, 1992). Other potent vasoconstrictors, such as endothelin, also contribute to the intense increase in peripheral vascular resistance (McMurray et al, 1992). Initially these changes are opposed by the cardiac endocrine system which produces atrial and brain natriuretic peptides

which have both natriuretic and vasodilator effects. The development of heart failure is an indication that these more favourable mechanisms have been overcome.

Ultimately as a consequence of this extensive compensatory activity, structural changes take place in the vascular arterioles with increasing stiffness of the vessels, morphological changes occur in skeletal muscle (Mancini et al, 1992) and respiratory function is affected with an increase in physiological dead space and airways obstruction (Sullivan et al, 1988). This vicious circle leads to further remodelling and ventricular dilation with a consequent reduction in cardiac output associated with electrical instability which ultimately leads to death either from progressive pump failure or suddenly as a result of arrhythmia.

1.1.9 Updated Definition of Chronic Heart Failure

Consequent on our growing awareness that chronic heart failure is not just an isolated cardiac response to a wide range of insults but is a condition with numerous metabolic and endocrine effects, perhaps a more suitable definition for the clinician is that proposed by Packer (Packer, 1988): "Chronic heart failure represents a complex clinical syndrome characterised by abnormalities of left ventricular function and neurohormonal regulation which are accompanied by effort intolerance, fluid retention and reduced longevity."

1.2 The Epidemiology of Chronic Heart Failure

The complexity of the epidemiology of chronic heart failure (CHF) stems from the fact that "heart failure" is not a diagnosis *per se* but a syndrome made up of symptoms and signs produced by cardiac dysfunction. The prevalence

and incidence of heart failure is, therefore, critically dependent on the criteria used to define its presence. In addition, since the syndrome of CHF occurs as a consequence of cardiac disease, the prevalence and incidence vary with the "population" under study. Thus it will occur more commonly in populations with a high prevalence and incidence of its precursors, coronary heart disease, hypertension and diabetes. However, all studies agree that CHF is common and that its prevalence and incidence are rising.

1.2.1 Prevalence of Chronic Heart Failure

Population Studies

Most of the epidemiological work on CHF has relied upon a "clinical diagnosis" for its detection. Eriksson et al, studied a cohort of 855 men, born in Gothenburg, Sweden, in 1913. Heart failure was detected from symptoms of breathlessness, signs of fluid retention and the need for digoxin and/or diuretic therapy. In this study, "manifest heart failure" had a prevalence of 2.1% at 50 years, 2.4% at 54 years, 4.3% at 60 years and 10.3% at 67 years (Eriksson et al. 1989). Similar figures were obtained from another European study from Germany with a CHF prevalence of 3% of the population i.e. 1.9 million people (Dinkel et al. 1989).

The largest epidemiological study to look at CHF in the community is from North America: the Framingham Heart Study, based in a small, geographically selected, semi-urban US population. It commenced in 1949 and has studied the prevalence and incidence of cardiovascular conditions in 5209 individuals who were aged 30-62 at enrolment. They diagnosed CHF

according to a clinical scoring system which included some objective evidence of cardiomegaly from a chest-X-ray. The reported prevalence was slightly lower than the European rates: 0.8% (ages 50-59), 2.3% (ages 60-69), 4.9%(ages 70-79) and 9.1% for those greater than 80 years (McKee et al. 1971,Kannel et al. 1988). Presumably the Framingham Study detected those with more advanced CHF.

In contrast to Framingham, which represents a rather atypical population, data from the National Health and Nutrition Examination Survey (N-HANES) described prevalence rates for CHF in the US general population of 2%, based on self reported heart failure, a clinical scoring system and chest-X-ray appearances in a screened population of 14,407 men and women aged 25-74 between 1971 and 1975 (Schocken et al. 1992).

Physician Records

In general, population prevalence rates for CHF detected from scrutiny of medical records and prescription data tend to be lower, as they focus on those who have disease which is severe enough to have reached medical attention and has crossed the threshold for therapeutic intervention.

In 1962-65, Gibson et al measured the prevalence of CHF in the white population in two rural US communities. "Heart Failure " was assessed by a physician's diagnosis. The study estimated the population prevalence rates to be 0.88% in one community and 1.2% in the other (Gibson et al. 1966).

In the UK, Parameshwar at al examined the clinical records of diuretic treated patients in three General practices in North West London. The prevalence of CHF was 0.39% overall, rising from 0.06% in those under 65 years to 2.8% in

those over 65 (Parameshwar et al. 1992b). Again the lower prevalence rates in this UK study reflect the application of "stricter" diagnostic criteria. More recent data from two primary care practices in Liverpool have indicated a higher prevalence rate of 1.5% which peaks at 8% for those over 65 years (Mair et al. 1996).

1.2.2 Prevalence of Left Ventricular Systolic Dysfunction

Studies documenting the prevalence of CHF in the general population using objective measures of LV function are, to date, limited for systolic dysfunction and almost non-existent for diastolic dysfunction. One would expect the prevalence rates for left ventricular systolic dysfunction to be higher in such studies than in those relying on clinical diagnosis as they have the potential to identify subjects with asymptomatic left ventricular systolic dysfunction- the precursor of CHF.

The Framingham Heart Study has published M-Mode echocardiographic data on their "offspring" cohort i.e. the children of the original study population and their spouses. In 1493 men, free of cardiovascular disease, 11.4% had an abnormal left ventricular end diastolic dimension (LVEDD≥5.6cm) and 5.1% had a reduced fractional shortening (FS≤30%). This subclinical left ventricular dilation and systolic dysfunction was associated with an increased risk of new cardiovascular diseases at subsequent follow up (Lauer et al. 1992).

More recent work from the Framingham Study has suggested that subclinical LV dilation (decreased fractional shortening by M-Mode echocardiography), which was found in 5.2% of men and 1.9% of women in a cohort of 4744

subjects free of myocardial infarction, did progress to CHF: there was an increased hazard ratio of 1.47(95% confidence intervals, 1.25 to 1.73) for the development of CHF obtained in the 11 year follow up with every one standard deviation increment in the left ventricular end diastolic dimension (Vasan et al. 1997b).

Gardin et al have also published work on subjects over 65 years, using a subjective assessment of left ventricular function and found it to be reduced in 6.8% of asymptomatic men and 1.8% of women (Gardin et al. 1995). Work is also now available from the Rotterdam Study indicating that 3% of subjects over 55 years have a fractional shortening <25% (Mosterd et al. 1997).

1.2.3 Prevalence of Diastolic Dysfunction.

Left ventricular dysfunction can, of course be due to diastolic dysfunction (or a combination of systolic and diastolic dysfunction). Indeed 36-42% of patients who have CHF diagnosed on clinical criteria have normal systolic function (Dougherty et al. 1984, Soufer et al. 1985). Thus, the population prevalence of diastolic dysfunction may be about forty percent of that attributable to systolic dysfunction. However, there is, as yet, no information on the prevalence of diastolic dysfunction in the " general population ".

1.2.4 Chronic Heart Failure and Left Ventricular Systolic Dysfunction In "High Risk" Populations

It is in post MI populations that the greatest prevalence rates for CHF are to be found. In the Framingham Study, 18% of patients with myocardial infarction developed CHF within five years; a ten year adjusted risk of heart

failure ten to twenty times that of the general population (Kannel et al. 1979, Kannel, 1987).

This study predated the use of thrombolytic therapy, which now results in more patients surviving acute myocardial infarction (Yusuf et al. 1988). In a more recent study of all patients with myocardial infarction in a District General Hospitai, heart failure developed, even if only transiently, in at least 35% (Stevenson et al. 1993).

Similarly, in the post thrombolytic era in the US, one of the largest post myocardial infarction trials of angiotensin converting enzyme inhibitors, the SAVE Trial, found that 40% of their population had evidence of left ventricular systolic dysfunction post MI (LVEF≤40%), 14% had CHF and 25% had asymptomatic left ventricular systolic dysfunction (Pfeffer et al. 1992). Similar figures were obtained in a European Post MI trial (TRACE) with 39% of subjects having a wall motion score index ≤1.2 (Kober et al. 1994).

Not surprisingly, the prevalence of CHF is also higher in those at most risk of developing myocardial infarction i.e. individuals with coronary artery disease. Objective information on LV function is now available from the Framingham Study, showing that LV dilation is present in 19 % of women and 23.2% of men with proven coronary artery disease (Galderisi et al. 1992).

1.2.5 Incidence of Chronic Heart Failure

At thirty four years of follow up in the Framingham Heart Study, the incidence rate for CHF was 2/1000 in persons aged 45-54 years rising to 40/1000 in men aged 85-94 (McKee et al. 1971). Using similar diagnostic criteria, Eriksson et al reported incidence rates for "manifest heart failure" for men of

1.5/1000, 4.3/1000 and 10.2/1000 at ages 50-54, 55-60 and 61-67- figures similar to Framingham (Eriksson et al. 1989). More recently Remes et al (using the Framingham clinical criteria for diagnosis) have reported the incidence of heart failure in rural Eastern Finland in men aged 45-74 at 4.1/1000- very consistent with the above studies (Remes et al. 1992). There are, however, no incidence data for heart failure diagnosed objectively by measurement of LV function.

1.2.6 Aetiology of Chronic Heart Failure and Left Ventricular Systolic Dysfunction

As alluded to earlier there is a myriad of possible causes of CHF and its principal antecedent, left ventricular systolic dysfunction. Their relative importance varies principally with geography such that it would be Chagas Disease in South America and hypertension in North American Blacks. There are four main data sources on the aetiology of left ventricular systolic dysfunction: (1) Population-based studies, (2) Physician records, (3) Hospital admissions and discharges, (4) Controlled Clinical Trials.

Population-based Studies

The Framingham Heart Study on publication of its 32 year follow up in 1971 claimed that hypertension was found in 77% of all the cases of CHF identified in contrast to ischaemic heart disease (IHD) which was present in only 30-45% (McKee et al. 1971). Throughout the 1980s there appeared to be a shift in the aetiology of CHF in the cohort. When the 44 year follow up data were made available, IHD had superseded hypertension and accounted for 55% of cases (although 31% had coexistent IHD and hypertension). Hypertension on

its own accounted for only 24% of the CHF discovered (Ho et al. 1993a). However that finding has been challenged in the latest Framingham analysis where the population attributable risk for hypertension and CHF was quoted at 39% for men and 59% for women (Levy et al. 1996). This apparent swing back to hypertension, however, should be treated with caution as the definition of hypertension in the Framingham study has changed from a blood pressure of >160/95mmHg until the 1980s when it dropped to >140/90mmHg. This will obviously increase its prevalence in the cohort.

Population-based studies other than Framingham have confirmed the dominance of IHD in the causation of CHF. Eriksson reported that 55% of those with manifest CHF had IHD, 48% had hypertension (Eriksson et al. 1989). The dual aetiology was also important with 79% having both risk factors. Interestingly, in this study, hypertension appeared to be a more potent correlate of latent CHF occurring in 52% of cases compared to 25% for IHD. IHD has also been confirmed as the principal aetiology of the heart failure identified in another European Population in Eastern Finland, occurring in 61% of cases (Remes et al. 1992).

Physician Records

Mair et al have confirmed from their study in another U.K urban population that IHD is the principal aetiology of the CHF identified in primary care (Mair et al. 1996).

It should be borne in mind that the aetiology of left ventricular systolic dysfunction from the above data sources is not completely accurate as the occurrence of dilated cardiomyopathy cannot be established due to the

impracticality of performing coronary angiography in such epidemiological studies.

Hospital Admissions

A similar pattern to the above has been confirmed in the UK for hospital admissions: of admissions to a district general hospital with CHF over a 6 month period with CHF, 41% had IHD and 6.4% were hypertensive (Parameshwar et al. 1992a).

Racial differences, even within so called Western, industrialised societies are also important. In a recent hospital-based study in the US, hypertension was the most common cause of symptomatic left ventricular dysfunction in blacks, IHD accounting for only 23% (Mathew et al. 1996).

Controlled Trials

Moving into the more select arena of clinical trials, Teerlink et al published a review of CHF Trials during 1989-90 involving 1861 patients. This confirmed the ascendancy of IHD in the aetiology of CHF, with 50.3% of enrolled subjects having this as the main cause (Teerlink et al. 1991). As expected in the hospital setting, idiopathic dilated cardiomyopathy gained more prominence accounting for 18.2% of cases. The major CHF treatment trials all have had the majority of their patients in the ischaemic category: 44% in VeHeft I (Cohn et al. 1986) and 73% in CONSENSUS 1 (Swedberg et al. 1987).

The only information we have for the aetiology of left ventricular systolic dysfunction comes from these trials. Regarding symptomatic left ventricular systolic dysfunction: 71% of subjects recruited into the treatment arm of

SOLVD had IHD, 42% were hypertensive (The SOLVD Investigators, 1991) and in the VeHeft II study, 53% had IHD, 48% were hypertensive and 35% were felt to have alcoholic cardiomyopathy (Cohn et al. 1991).

Information on the causation of asymptomatic left ventricular systolic dysfunction is very limited. There is some available from the prevention arm of SOLVD showing a similar pattern to symptomatic left ventricular systolic dysfunction in that 83% of patients had IHD, 37% were hypertensive and 9% were thought to have idiopathic cardiomyopathy (The SOLVD Investigators, 1992).

Although the absolute contribution of the various aetiologies varies a little in the data discussed, the general impression is that IHD is the most important cause of CHF and left ventricular systolic dysfunction, hypertension also has a major role, the two often coexist and there appears to have been a shift from hypertension to IHD as the principal aetiology over the last 25 years.

1.2.7 Importance of Chronic Heart Failure and Left Ventricular Systolic Dysfunction

The importance of CHF and its antecedent left ventricular systolic dysfunction can be considered by examining their effects on mortality, morbidity and cost.

Mortality: Population-based studies

Heart Failure is a fatal condition with a mortality which exceeds many malignancies. In the Framingham Study the probability of dying within five years of the onset of heart failure was 62% for men and 48% for women (McKee et al. 1971). "The Men Born in 1913" study provided information on

mortality rates in less severe heart failure with a five year mortality rate of 26% in men with mild to moderate CHF and 10% in those with "latent heart failure" (Eriksson et al. 1989). The more recent NHANES survey has confirmed the grave prognosis with a 10 yr. mortality of 54% in men and 38% in women over the 25-74 age group to which this thesis pertains (Schocken et al. 1992).

Mortality of CHF and Left Ventricular Systolic Dysfunction: Clinical Trials

Recent therapeutic advances, in particular, the angiotensin-I-converting enzyme inhibitors (ACEI), have made only a modest impact on that prognosis. In the CONSENSUS 1 Study, one year mortality in the NYHA Class IV CHF patients treated with enalapril was still 36% compared to 52% in the placebo group (Swedberg et al. 1987) In the same vein, NYHA Class II-III patients in the SOLVD Treatment Trial placebo group had a mortality of 40% at four years into follow up (The SOLVD Investigators, 1991). The treatment arm mortality remained considerable (though significantly reduced) at 35%. The post MI LV systolic dysfunction trial TRACE still exhibited high mortality rates of 42.3% (placebo group) and 34.7% (ACEI group) at 4 years (Kober et al. 1995). In contrast, the annual mortality in patients with asymptomatic left ventricular systolic dysfunction is only 4% (The SOLVD Investigators, 1992) which gives considerable hope that earlier detection and treatment of CHF in its asymptomatic phase will be of benefit.

Mortality of Diastolic Dysfunction

Epidemiological data regarding the natural history of diastolic heart failure is very limited, as all the recent heart failure treatment trials have only studied patients with systolic dysfunction. In five years of follow up in the Veterans Administration Co-operative Study Group (The Ve-Heft Study) (Cohn and Johnson, 1990), no significant decline in ejection fraction occurred in the subgroup with normal systolic function. The group with diastolic dysfunction had a significantly lower annual mortality rate of 8% versus 19% in those with a reduced ejection fraction. However, recent population-based data from the Mayo clinic have suggested that the outlook from diastolic dysfunction is no better than that of systolic dysfunction (Senni et al. 1997).

Morbidity

CHF is associated with considerable morbidity. The annual hospitalisation rate for those with CHF approaches 45% (The SOLVD Investigators, 1991). Parameshwar et al found that CHF accounted for 4.9% of all medical and geriatric admissions in a District General Hospital in North West London (Parameshwar et al. 1992a). Once in hospital, these patients had a long stay with an average hospitalisation time of 16.7 days. Similar data for Scottish Hospitals revealed heart failure to account for 4.1% of all general medical and cardiology admissions (McMurray et al. 1993).

Data are available for hospitalisation for CHF from the clinical trials for patients with symptomatic left ventricular systolic dysfunction showing that 36.6% of placebo subjects in the SOLVD treatment arm were hospitalised over a four year period as compared with 25.8% in the ACEI group (The

SOLVD Investigators, 1991). For asymptomatic left ventricular systolic dysfunction, the rates are less with 21.5% of the placebo group and 14.5% of the ACEI group requiring admission for CHF over 4 years in the prevention arm of SOLVD (The SOLVD Investigators, 1992). Similarly in post MI left ventricular systolic dysfunction from the SAVE Study, 17% of placebo and 14% of captopril treated patients were admitted over a four year period (Pfeffer et al. 1992).

In addition, CHF causes more impairment of quality of life than any other chronic medical disorder (Stewart et al. 1989). In the treatment arm of SOLVD (Gorkin et al. 1993) and in the "Men Born in 1913 Study" mild and moderate CHF was associated with less energy, lower fitness levels and more physical complaints (Eriksson et al. 1988). Consequent to its high morbidity and high hospitalisation rate, it is no surprise that CHF is a health problem with major economic implications for health care delivery systems (McMurray and Hart, 1993). In the UK in 1996, the annual expenditure for CHF was £360 million, which was 1.2% of total health care expenditure, 60% of which was attributable to hospitalisation (McMurray and Davie, 1996).

1.2.8 Trends In CHF Epidemiology

Epidemiological studies agree that, despite differences in definition, incidence and prevalence rates, heart failure is a growing world-wide health problem. This is, in part, due to the increasing longevity of the population in industrialised countries. Two reports from the US. suggest that hospitalisation rates for CHF have been rising (Gillum, 1987,Ghali et al. 1990). Similarly, in Scotland, the number of hospitalisations for CHF rose by 6% between 1980-

1990, such that the number of admissions for CHF now nearly equals those for myocardial infarction (McMurray et al. 1993).

1.3 Exercise Testing in Heart Failure

The definition of heart failure used at the outset of this thesis alludes to a central pump failing to respond to the needs of the tissues, principally, in their requirement for oxygen. Consequently, the manifestations of pump malfunction in heart failure are more pronounced on exercise. The cardiac response to exercise, therefore, is in some ways fundamental to any pathophysiological dissection of CHF.

Thus, the cardinal symptoms of CHF, breathlessness and muscle fatigue occur, at least initially, on exertion. We would therefore expect exercise testing to be as valuable for the clinician, as it is for the physiologist in the diagnosis and assessment of heart failure.

1.3.1 Oxygen Uptake and Left Ventricular Dysfunction

The best indicator of aerobic capacity, the maximal oxygen uptake (VO_2 max), measured during incremental cardiopulmonary exercise testing, is reduced in subjects with symptomatic left ventricular systolic dysfunction. However, a true maximal oxygen uptake, where the work rate of the subject increases despite a plateau in oxygen consumption is rarely achieved in heart failure subjects (Lipkin et al. 1985). Since these patients generally stop prior to this with muscle fatigue or breathlessness, the peak oxygen uptake is more usually quoted. The peak oxygen uptake is similarly reduced in subjects with symptomatic left ventricular systolic dysfunction. It reflects the severity of symptoms and is reproducible (Weber et al. 1984).

Not only is the peak oxygen uptake reduced in symptomatic left ventricular systolic dysfunction, it is now also known to be diminished in asymptomatic left ventricular systolic dysfunction. Data from the prevention arm of the SOLVD trial show that asymptomatic patients, on no cardiac medication, who had left ventricular ejection fractions≤ 35% had a significantly reduced peak VO_2 compared to controls (LeJemtel et al. 1994). Indeed, the mean exercise duration in subjects with asymptomatic left ventricular systolic dysfunction was 291 seconds, nearly five minutes less than normal, age and sex - matched controls.

Exercise capacity is also reduced in diastolic heart failure. Kitzman and colleagues have studied subjects who have at least one episode of symptomatic heart failure who had preserved LV systolic function, and found they had a diminished peak VO_2 compared to normal controls (Kitzman et al. 1991).

Exercise testing would, therefore, appear to be useful in the evaluation of heart failure, be it symptomatic or asymptomatic or due to systolic or diastolic dysfunction. However, there are some drawbacks which have to be borne in mind when considering its role in the assessment of CHF. These relate to the poor correlation between measures of exercise capacity and other commonly used methods of classifying CHF.

1.3.2 Relationship Between Measures of Effort Capacity and Other Markers of Chronic Heart Failure.

Exercise variables correlate poorly with the New York Heart Association Category (Franciosa et al. 1979). In addition, there is, at best, only a weak

relationship between resting haemodynamic measures of LV function (cardiac index, pulmonary capillary wedge pressure or angiographic ejection fraction) and measures of exercise performance (Franciosa et al. 1981). Finally, there is essentially no relationship between commonly used resting echocardiographic methods of determining LV function, the LV ejection fraction or left ventricular end diastolic dimension, and exercise capacity (Weber et al. 1984).

The poor relationship between measures of LV function and effort capacity in left ventricular systolic dysfunction is hardly surprising as many factors other than central pump function affect exercise capacity in heart failure subjects. We know that CHF subjects have an abnormal ventilatory response to exercise with an increase in dead space ventilation (Sullivan et al. 1988). There are also changes in the periphery with alterations in skeletal muscle biochemistry leading to an early acidosis on exercise testing (Wilson et al. 1985). There are effects of secondary physical deconditioning causing changes in skeletal muscle morphology (Mancini et al. 1992, Starling et al. 1981). There is impaired nutritive flow and an increase in peripheral vascular resistance (Zelis et al. 1974).

Despite these drawbacks, maximal or peak oxygen uptake measured from an incremental exercise protocol, in ambulant patients, is widely accepted to a good, if not, the best measure of the severity of CHF. Although resting LV function measurements do not equate with exercise parameters, functional classifications of maximum oxygen uptake do correlate well with exercise haemodynamic measures of LV function. Weber and colleagues have

classified heart failure subjects into four categories based on maximal oxygen uptake (Weber and Janicki, 1985). They found, that on exercise testing, these categories correlated well with cardiac index and wedge pressure. Patients in the poorest oxygen consumption category had a blunted increase in cardiac index with exercise, compared to those with less impairment of aerobic capacity. They also had a higher wedge pressure at peak exercise compared to those groups with superior oxygen uptake. Oxygen uptake is, therefore, useful in grading the severity of CHF.

Thus, exercise testing does have a diagnostic role in evaluating and clarifying symptoms in CHF and in grading its severity. This can be done either by the measurement of maximal or peak oxygen uptake or by measuring exercise duration, provided that in the exercise protocol used, exercise duration adequately reflects oxygen consumption.

The correlation between exercise duration and oxygen consumption varies between exercise protocols. When oxygen consumption is plotted against exercise duration in both normal volunteers and CHF subjects using the Standardised Exponential Exercise Protocol (STEEP) (both for normals and CHF subjects) there is a good linear relationship between the values. Using such a protocol it would be possible to regard exercise duration as a reasonable surrogate for peak oxygen uptake (Riley et al. 1992). This is the protocol used in this thesis.

1.3.3 Role in Assessment of the Aetiology of Left Ventricular Systolic Dysfunction

The management of CHF depends on its aetiology. Therefore, a cause should always be sought. Exercise testing has an obvious role in the assessment of the main aetiological factor in left ventricular systolic dysfunction, ischaemic heart disease.

As well as guiding medical management of ongoing myocardial ischaemia, it is also helpful in detecting those patients who would benefit from revascularisation surgery. Bounous and colleagues have demonstrated, in nine years of follow up, that in subjects with left ventricular systolic dysfunction, whether it is mild, moderate or severe who have severe coronary artery disease, there is a survival benefit to be gained from revascularisation surgery compared to medical management (Bounous et al. 1988).

1.3.4 Role in Prediction of Prognosis

Exercise testing also has a role in estimating prognosis in heart failure.

The poorer survival of CHF subjects who have reduced effort tolerance on exercise testing has been confirmed by some of the larger heart failure treatment trials. In both the Ve Heft trials, with, in total over 1400 men, maximum oxygen consumption and exercise duration were independent predictors of mortality in up to 5 years of follow up (Cohn et al. 1993).

Roul and colleagues have studied 75 subjects with CHF in NYHA categories II and III and found that those who had a peak oxygen uptake of less than or equal to 14 mls/kg /min have a significantly higher mortality than those with a greater aerobic capacity (Roul et al. 1994). The figure of 14mls/kg/min has

been suggested by Mancini and others as one at which cardiac transplantation should at least be considered (Mancini et al. 1991).

Although in this study peak oxygen consumption was the best predictor of mortality exercise duration also correlated with death. The authors suggested that patients could be followed up by exercise duration providing the exercise protocol satisfactorily reflected oxygen consumption.

Although the relationship between exercise parameters and left ventricular systolic dysfunction has been extensively studied in patient populations, there is no population-based study examining this. The work presented in Chapter 5 addresses this issue.

1.4 The Natriuretic Peptides

The natriuretic peptides comprise a family of three hormones, principally produced by the heart. They cause natriuresis, diuresis and vasodilation and play a major role in sodium and volume homeostasis in health and disease.

The first of these peptides to be discovered, and the most extensively studied, is atrial natriuretic peptide. It is a 28 amino acid peptide, synthesised and secreted, predominantly by the cardiac atria (Kangawa and Matsuo, 1984). It is stored in the myocyte as a 125 amino acid prohormone and on secretion, is cleaved into an N-terminal fragment (N-ANP) of 98 amino acids and the biologically active C-terminal-ANP (Singer et al. 1996). The half life of ANP is considerably shorter (2.5 mins) than N-ANP. N-ANP is thus more easily measured (Singer et al. 1996, Wei et al. 1993).

A second natriuretic peptide, brain natriuretic peptide (BNP), was discovered in 1988 (initially named owing to its first description in porcine brain). Its

predominant site of origin has subsequently been shown to be the ventricular myocardium (Yasue et al. 1994,Yoshimura et al. 1993). It is a 32 amino acid peptide similar in structure to ANP (Mukoyama et al. 1990).

The third peptide, CNP, is mainly

found in the central nervous system and vascular endothelium and appears to have limited natriuretic and vasodilator properties (Hunt et al. 1994).

1.4.1 Production

The main trigger for the production of both ANP and BNP is stretching of the atrial and ventricular walls (Kinnunen et al. 1993). While there is a relationship between atrial pressure and plasma ANP concentration, atrial wall stress and stretch are the predominant stimuli for ANP release (Schuster et al. 1995). Similarly, BNP is secreted, principally by the ventricles in response to ventricular dilation (smaller amounts are also released from the atria) (Yasue et al. 1994,Yoshimura et al. 1993). Both ANP and BNP are detectable in the plasma of normal subjects at picomolar concentrations.

1.4.2 Exertion of Action

The natriuretic peptides produce their actions via three different receptors; A, B and C (Nakao et al. 1992). The A and B receptors cause increased production of cyclic GMP. The C receptor acts as a clearance receptor but may also exert biological actions via mechanisms other than cGMP (Luscher, 1994). All three receptors are widely distributed and are found in the kidney, vascular endothelium, adrenals, the central nervous system as well as in the heart (Califf and Bengtson, 1994).

1.4.3 Clearance

Natriuretic peptides are removed from the circulation by two main mechanisms, firstly via receptor mediated endocytosis and secondly through degradation by the enzyme neutral endopeptidase (Townend and Littler, 1993).

1.4.4 Actions

Both ANP and BNP produce natriuresis and diuresis by a direct effect on the collecting duct and through actions on the glomerular and tubular cells. They also inhibit the actions of anti-diuretic hormone (Sunman and Sever, 1993). Importantly, they also interact with other neurohormonal mechanisms. ANP is known to antagonise the renin-angiotensin-aldosterone system by inhibiting renin production, decreasing angiotensin converting enzyme activity and inhibiting aldosterone release by angiotensin II (Kurtz and Della Bruna, 1986, Berning et al. 1992, Gregor et al. 1984). ANP also decreases sympathetic nervous system activity (Dubin et al. 1990) (Interestingly BNP does not and can increase noradrenaline levels; but its other actions are similar). Both ANP and BNP inhibit the release of the potent vasoconstrictor, endothelin (Akhras and Jackson, 1991). The effects of ANP and BNP within the heart are less well documented but ANP is known to be a coronary vasodilator.

In contrast with the other hormones, CNP, is thought to act as a neurotransmitter in central cardiovascular control systems and may exert paracrine effects on vascular growth. It is not a vasodilator or diuretic (Maggioni et al. 1991).

1.4.5 Pathophysiology

Both the C and N terminals of ANP are predominantly secreted by the atria in response to the stretch which accompanies the increased left atrial pressure associated with the full blown syndrome of chronic heart failure (Wei et al. 1993). The circulating concentrations of both these peptides are raised in patients with symptomatic left ventricular systolic dysfunction i.e. CHF (Gottlieb et al. 1989). The levels of N-ANP are higher, reflecting its reduced renal clearance. More recently BNP concentrations have also been shown to be elevated in patients with symptomatic left ventricular systolic dysfunction (Yasue et al. 1994). The absolute ANP and BNP levels correlate with other commonly used markers of the severity of CHF including haemodynamic parameters, indices of systolic function and the New York Heart Association Class (Gottlieb et al. 1989, Yasue et al. 1994). Mean plasma concentrations of N-ANP and BNP are also raised in subjects with asymptomatic left ventricular systolic dysfunction (Lerman et al. 1993, Motwani et al. 1993). Other conditions are also associated with increases in the natriuretic peptides (though much smaller) including, left ventricular hypertrophy (BNP) (Kohno et al. 1992), diastolic dysfunction (BNP) (Clarkson et al. 1996), renal impairment (both ANP and BNP) and advancing age (both ANP and BNP) (Wei et al. 1993).

The finding of increased circulating levels of these hormones in left ventricular systolic dysfunction has led to speculation about their usefulness in the diagnosis, prognosis, therapeutic monitoring and modulation of this condition.

1.4.6 Diagnosis: in Patient Groups

Symptomatic Left Ventricular Systolic Dysfunction

Symptoms and signs lack both sensitivity and specificity in the diagnosis of CHF. In contrast to this, natriuretic peptides have been shown to be useful in differentiating heart failure as the cause of dyspnoea in patients presenting with acute breathlessness (Davis et al. 1994). BNP appears to be a better diagnostic marker than ANP: a BNP concentration of ≥22pmol/l giving a sensitivity of 93% for diagnosing heart failure and for the detection of left ventricular systolic dysfunction, it had a sensitivity of 80% with a specificity of 70%.

Asymptomatic Left Ventricular Systolic Dysfunction

Both N-ANP (Lerman et al. 1993) and BNP (Motwani et al. 1993, Omland et al. 1996b) are also raised in patients with asymptomatic left ventricular systolic dysfunction. Lerman et al found that N-ANP at a concentration of >54pmol/l had a sensitivity of 90% and specificity of 92% for detecting symptomless left ventricular systolic dysfunction in subjects undergoing diagnostic cardiac catheterisation (Lerman et al. 1993).

Left Ventricular Systolic Dysfunction (Symptomatic or Asymptomatic) Post Myocardial Infarction

Motwani et al (Motwani et al. 1993) demonstrated that plasma BNP can identify those with significant left ventricular systolic dysfunction post myocardial infarction who would benefit from ACE inhibition. This work has been corroborated by others (Choy et al. 1994, Omland et al. 1996a) indicating that BNP has a sensitivity of 84% in detecting left ventricular

systolic dysfunction post infarct (greater than that of ANP which was 64% sensitive). These peptides, therefore, have the potential to assist in risk stratification post MI to determine groups likely to benefit from ACE inhibition.

1.4.6 Prognosis

Giving the apparent relationship between BNP concentration and left ventricular function, it is perhaps not surprising that BNP has been shown to be of value in predicting prognosis in cardiovascular disease. In a recent study carried out in subjects post acute myocardial infarction, BNP was strongly and independently associated with long term survival (Omland et al. 1996a). This work has now been extended to the general population, where BNP has been shown to predict mortality in elderly subjects (85 years) whether or not they have cardiovascular disease (Wallen et al. 1997).

Atrial natriuretic peptide (particularly N-ANP) has also been shown to predict outcome following myocardial infarction in terms of survival or the development of heart failure (Hall et al. 1994). However, when C-ANP, N-ANP and BNP have been compared in this regard, although all three peptides are powerful predictors of mortality on univariate Cox proportional hazards modelling, in a multivariate model, only BNP provided additional prognostic information beyond the left ventricular ejection fraction (Omland et al. 1996a). Thus, elevated concentrations of natriuretic peptides and in particular, BNP should help to identify those at highest risk who require specific treatment.

1.4.7 Monitoring of Treatment

As levels of the natriuretic peptides correlate with other commonly used markers of the severity of CHF and left ventricular systolic dysfunction, they

may also have a role in guiding the effectiveness of therapy in left ventricular systolic dysfunction. There is evidence showing that treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) reduces atrial natriuretic peptide levels early after myocardial infarction and during long term treatment in left ventricular systolic dysfunction (Bonarjee et al. 1995, McMahon et al. 1983). More limited data is available for BNP indicating lower plasma levels in subjects with left ventricular systolic dysfunction post MI treated with ACE inhibition (Motwani et al. 1993).

Murdoch et al have also conducted a small study randomising subjects with CHF to either standard therapy guided by clinical parameters or to adjustments in treatment driven by BNP levels (aiming to normalise plasma BNP). While there was no significant difference in haemodynamics between the two groups, those receiving BNP driven therapy had a more favourable neurohormonal profile (Murdoch et al 1997a).

Much work is needed before natriuretic peptides are in routine clinical use in monitoring the treatment of left ventricular systolic dysfunction but preliminary work suggests that they may have a role in the future as "biochemical Swan Ganz catheters" or HbA1 equivalents.

1.4.8 Therapeutic Modulation

As the endogenous response of the body to fluid overload, the natriuretic peptide system is also being exploited therapeutically in the management of left ventricular systolic dysfunction. This approach may have advantages over conventional therapy. Unlike loop diuretics and many vasodilators, natriuretic peptides cause inhibition rather than stimulation of the renin

angiotensin system. In addition, ANP may also reduce cardiac ischaemia and modulate vascular growth. The neutral endopeptidase inhibitor, candoxatril, which increases both ANP and BNP concentrations has been shown to produce a natriuresis in CHF similar to frusemide but with a more beneficial neurohormonal profile (Northridge et al. 1992). A larger, longer term, study using candoxatril also produced an improvement in effort capacity in subjects with CHF (Newby et al 1997). In addition, intravenous infusions of both ANP (Cody et al. 1986) and BNP (Marcus et al. 1996) cause diuresis, natriuresis and alter haemodynamics favourably in heart failure.

The natriuretic peptide system forms a complementary cardiovascular control system which offsets the activity of the renin-angiotensin-aldosterone system in left ventricular systolic dysfunction. Our knowledge, so far, of the peptide hormones themselves points to them having important roles in the diagnosis, prediction of prognosis and in treatment monitoring of left ventricular systolic dysfunction. The usefulness of these peptides to detect left ventricular systolic dysfunction in the general population is, however, unknown and is the basis of the work presented in Chapter 6 of this thesis.

1.5 The Angiotensin-I-Converting Enzyme Insertion/Deletion Polymorphism

Activity of the zinc metalloprotease, angiotensin converting enzyme, produces the octapeptide angiotensin II which is thought to have an important role in the pathophysiology of heart failure, cardiac remodelling post myocardial infarction and the development of left ventricular hypertrophy. The gene encoding the angiotensin converting enzyme is located on Chromosome 17q

(Hubert et al. 1991). It contains a polymorphism (ACE I/D) consisting of the presence or absence of a 287bp fragment (Alu repetitive sequence) in intron 16 (Rigat et al. 1992). The polymorphism most probably represents a neutral marker for a functional variant explaining 25-44% of the interindividual variability of plasma ACE activity (Cambien et al. 1994). Homozygous subjects for the D allele have circulating ACE concentrations nearly double that of II individuals (Cambien et al. 1994).

1.5.1 Myocardial Infarction

Cambien et al (Cambien et al. 1992) first reported on the association between the DD genotype and the risk of MI in a large case-control study from three French and one Northern Irish MONICA centres: the prevalence of DD was 1.34 times higher in the cases than the controls. Interestingly, the odds ratio was higher in "low risk" subjects (those with lower body mass indices and apolipoprotein B levels). Several other studies have confirmed this observation, including an autopsy study on subjects dying suddenly with MI in Belfast (Evans et al. 1994). However, not all reports are in agreement: a relatively small Norwegian study found the DD genotype to be less common in men with MI (Bohn et al. 1993).

Other studies have had broader endpoints including angina and "prevalent coronary heart disease" and have found mixed results regarding the association of the DD genotype with increased risk (Meittinen et al. 1994, Mattu et al. 1995). In particular two large studies from the US have provided divergent results. The Physicians Health Study (Kreutz et al. 1993) reported no association of the DD genotype with MI or revascularisation. Whilst this is

a prospective study, it is however, a highly selected population (5% of invitees were recruited) with a low event rate. An angiographic study from Utah (Ludwig et al. 1993), did find the DD genotype to be increased in men with a history of prior MI, again with the relationship being stronger in those traditionally at low risk. Several other European Studies support the DD risk association (Ossei-Gerning et al. 1995, Ahnve et al. 1995) and several from Japan suggest a much stronger association of IHD with the DD genotype (Zhao et al. 1994, Nakai et al. 1994).

With evidence looking slightly stronger for the association with the I/D polymorphism and MI risk, it has been suggested that publication bias has led to a false assumption. Recent evidence has shown that positive studies tend to be small and the larger studies, negative (Samani et al. 1996). A study conducted in this thesis allows further dissection of the association of the DD genotype with IHD and MI in a large cross-sectional, study population.

1.5.2 Hypertension

At the population level, hypertension is one of the most important risk factors for CHF. While there is relatively little evidence linking essential hypertension with the ACE genotype, only one small Australian study being positive (Harrap et al. 1993), there is now good evidence to link electrocardiographic LVH (Schunkert et al. 1994) and LV mass (Perticone et al. 1997) with the DD genotype.

1.5.3 Cardiac Failure

There is only the indirect evidence presented above to indicate a possible role for the ACE I/D polymorphism in heart failure, by assuming that its association

with IHD and hypertension, the main risk factors for CHF, will implicate it in their final manifestation. There is one report showing that the DD genotype was more frequent in subjects with ischaemic and dilated cardiomyopathy (Raynolds et al. 1993). There is, however, no population-based work on left ventricular systolic dysfunction relating to the ACE genotype. Part of this thesis addresses that question.

1.6 Aims of the Thesis

The introduction has highlighted the need for a substantial reappraisal of the epidemiology of CHF in the 1990s, not only for scientific purposes but to inform modern medical practice. The previous large population-based studies have relied on a clinical diagnosis of CHF, which we know can be unreliable. Epidemiological data on left ventricular systolic dysfunction is very limited, and there is none in the world on asymptomatic left ventricular systolic dysfunction, using a meaningful echocardiographic measurement. In addition, the aetiology of CHF may have changed since the major studies reported. With this in mind the aims of this thesis were to:

1 Determine the prevalence of left ventricular systolic dysfunction, both symptomatic and asymptomatic in an urban population (Chapter 3)

2 Ascertain the aetiology of the left ventricular systolic dysfunction, identified (Chapter 4)

3 Examine the effect of left ventricular systolic dysfunction on effort capacity (Chapter 5)

4 Test the usefulness of the natriuretic peptides in detecting left ventricular systolic dysfunction. (Chapter 6)

5 Study the relationship between the ACE I/D polymorphism, ischaemic heart disease and left ventricular systolic dysfunction. (Chapter 7)

Chapter 2

METHODS

2.1 Population.

2.1.1 Parent Cohort

The theoretical study population was all men and women aged 25-74, living in the City of Glasgow, North of the River Clyde (Tunstall-Pedoe et al. 1994, Smith et al. 1990). A random sample of this population were invited to attend the Third Glasgow MONICA Population Coronary Risk Factor Survey in 1992 (MONICA 3), using a two stage random sampling method. Firstly 30 family practitioners were randomly selected from the 210 in the area. Secondly, patients were randomly selected from each ten year age/sex band from 25-74 years in proportion to the doctor's list of patients. Oversampling to allow for non response was carried out. The response rate in that study was 67%.

2.1.2 Study Cohort

To recruit 30 family practitioners, 36 were invited to participate. Two were excluded (<200 patients each) and four refused. A total of 1952 men and 1889 women were invited to attend the Third Glasgow MONICA Coronary Risk Factor Survey (MONICA 3). Three hundred and thirty nine men and 250 women were not resident at the address held by the family practitioner and remained untraceable despite various searches; 138 men and 72 women were otherwise ineligible because of age or place of residence. Nine hundred and twenty seven men and 1031 women finally attended- a response rate among those eligible of 61.8% for men and 65.8% for women. The response rate varied by age, sex and social class with the youngest and least affluent groups in both sexes having the poorest response. The social class structure of the responders was similar to that of the population (which is skewed

towards the socioeconomically deprived) and the response rate is similar to that in other epidemiological studies in urban populations (Murray et al. 1995). Of the 1993 MONICA 3 responders invited to the present study, 1640 attended (83%). The response rate was 87% for men and 83% for women. This present sample is representative of the parent cohort in all relevant criteria with the exception that the attendees were more affluent and there were fewer smokers. The prevalence of coronary heart disease and hypertension was the same as that of the parent cohort.

2.1.3 Response Rate by age and sex.

The numbers attending did not differ significantly between the age sex groups with the exception of a statistically significant decrease ($p<0.01$, Chi Squared) in attendance in the oldest age band. (see Table 2.1). The age range has been kept in the original decades from 25-74 years even though they were screened 9 months to one years after their attendance at MONICA 3

Table 2.1: Attendance by age and sex

AGE GROUP (yrs)	**MALE %** (n)	**FEMALE** % (n)
25-34	93% (128)	87% (132)
35-44	82% (153)	85% (169)
45-54	96%. (161)	74% (183)
55-64	82% (174)	91% (172)
65-74	74% (181)	69% (188)

2.2 Echocardiogram

Standard two-dimensional, colour and Doppler echocardiography (Acuson 128) was performed with subjects recumbent at approximately 40 degrees, in the left lateral position. ECG electrodes were applied to produce a concurrent ECG tracing with a predominant negative deflection. Images were stored on videotape and analysed on line.

2.2.1 Left Ventricular Ejection Fraction

The left ventricular ejection fraction was obtained using the biplane disc summation method (Simpson's Rule) (Schiller et al. 1979) from the apical four and two chamber views. The endocardium (defined as the innermost black-white interface) was manually traced round using a tracker ball in diastole (the onset of the R wave on the ECG) and systole (the smallest left ventricular volume), in triplicate, in both the apical two and four chamber views). The papillary muscles were considered to be part of the ventricular cavity. Each ejection fraction calculated was a mean of three cardiac cycles (excluding ectopic, pre or post ectopic beats). Echocardiograms were deemed acceptable in terms of quality if 80% or more of the endocardium was visible.

2.2.2 M-Mode Measurements

All M-Mode measurements were made on three consecutive cardiac cycles (where possible) from the parasternal long axis view. They were not performed on ectopic, pre or post ectopic beats. Diastole was defined as above and systole as the point at which the furthest anterior motion of the posterior wall of the left ventricle occurred. M-Mode echocardiograms were

analysed according to the American Society of Echocardiography leading edge to leading edge methodology (Sahn et al. 1978). To ensure adequate quality control, the criteria of Schieken et al (Schieken et al. 1979) were used to determine acceptable technical quality for M-Modes i.e.:(1) the generation of a single dominant line representing the interface being imaged, (2) the demonstration of continuous interface lines at least 5mm in length at the point of measurement, (3) the demonstration of interfaces with the wall motion characteristic of the specific cardiac structure being imaged.

The following M-Mode measurements were made: (1) Left ventricular end diastolic dimension (LVEDD), (2) Left ventricular end systolic dimension (LVESD), (3) Interventricular thickness in systole (IVSs) and diastole (IVSd), (4) Left ventricular posterior wall thickness in systole (LVPWs) and diastole (LVPWd).

2.2.3 Doppler Echocardiography

The mitral forward flow was obtained using Pulsed Wave Doppler after positioning the callipers between the tips of the mitral valve leaflets in the apical 4 chamber view. Aortic forward flow was determined using continuous wave Doppler recording in the apical 5 chamber view. Doppler measurements were made on five wave forms to minimise respiratory influences. For Doppler peak velocity and flow velocity integrals, the spectral areas were traced round using the peak velocity correction (Benjamin et al. 1992) i.e. the outer edge of the spectral envelope. Measurements were made from beats demonstrating the following characteristics: (1) highest peak

velocity, (2) narrowest spectral dispersion and (3) the most normal contour appearance.

Transmitral Doppler waveforms were considered inadequate if: (1) the angle between the Doppler beam and the mitral waveform was ≥30°, (2) the sample volume was inadequately positioned, (3) the Doppler signal transmitted was too indistinct or (4) there was a tachycardia i.e. a heart rate greater than 100 bpm

"A" wave measurements were obviously impossible in the presence of atrial fibrillation.

If mitral incompetence was seen on colour flow, the extent of the incompetence was assessed by mapping the extent of the jet into the left atrium using pulsed wave Doppler (PW). A semi-quantitative scale was used dividing the left atrium into four equal sectors. Mild mitral incompetence (MR) was said to be present if the PW jet did not extend more than half way back into the left atrium during systole. Moderate MR was defined as the PW jet extending to the third quarter of the left atrium and severe MR if the jet could be detected in the quarter of the left atrium most distal to the mitral valve. Significant mitral incompetence was taken as anything other than mild MR.

2.2.4 Significant Valvular or Structural Heart Disease

Echocardiograms were analysed subjectively in real time and deemed to be significantly abnormal (and therefore excluded from the derivation of the normal range for the left ventricular ejection fraction) if they demonstrated any of the following abnormalities: a ventricular or atrial septal defect, hypertrophic

obstructive cardiomyopathy (see derived echo measurements), a left ventricular aneurysm, cor triatiatum, a pericardial effusion, contained a prosthetic valve, had a bicuspid aortic valve, or had any degree of mitral (pressure half time >120ms) or aortic stenosis (gradient>20mmg), or greater than mild mitral or aortic regurgitation.

2.2.5 Derived Echocardiogram Measurements

Fractional Shortening (FS) % =

$$\frac{\text{LVEDD-LVESD}}{\text{LVEDD}} \times 100$$

LV Mass (grammes)

$=1.04[(IVSd+LVEDD+LVPWd)^3-LVEDD^3]-13.6$

This was calculated using the Penn Cube formula (Devereux et al. 1986). LV Mass index was computed by dividing the LV mass in grammes by height in metres.

LV Ejection Fraction (%)

$$\frac{\text{LV end diastolic volume-LV end systolic volume}}{\text{LV end diastolic volume}} \times 100$$

The LV systolic and diastolic volumes were determined using the Simpson's biplane 20 segment disc summation method (Schiller et al. 1979).

Aortic pressure gradient (mmHg)

$=4\times$aortic peak velocity $(m/s)^2$

Significant aortic stenosis was taken as a gradient >20mmHg.

Aortic incompetence as seen by Colour Doppler was deemed to be important if it was moderate or severe as measured by the presence of a deceleration slope of >2.5m/s^2.

Mitral stenosis was diagnosed if there was a pressure half time of the E wave was >120ms.

Hypertrophic obstructive cardiomyopathy was said to be present if there was hypertrophy of the septum disproportionate to that of the posterior wall: the ratio of the IVSd:LVPWd being>1.3.

Mitral valve prolapse was defined as an excursion of a mitral valve leaflet of more than 3mm beyond the mitral valve annulus towards the left atrium.

2.2.6 Intraobserver and Interobserver Variation

Quantitative echocardiogram analysis was carried out by a single observer (myself). A random sample of 10% was reanalysed, blind to the first reading, by the same observer for the calculation of the intraobserver variation of measurements and a separate 5% random sample analysed by a second observer for the determination of the interobserver variation of the measurements.

2.3 Interview and Questionnaire

All subjects completed a questionnaire giving demographic details, current medication, a history of physician diagnosed myocardial infarction, angina, or diabetes mellitus, their smoking status (current, never or ex) and answered

the Medical Research Council Breathlessness questions (Fletcher et al. 1959).

2.4 Blood Pressure

Blood pressure was taken as a mean of two readings, measured sitting (after five minutes rest), in the right arm, using a random zero sphygmomanometer.

2.5 Body Mass Index

Subjects were measured, without their shoes and heavy outer garments, using a stadiometer on a hard surface. The participant had their back to the ruler, the back of the head, back, calves, buttocks and heels were touching the upright with the feet together. The top of the external auditory meatus was level with the inferior margin of the bony orbit. The triangle on the height rule was placed on the head so the hair was pressed flat. Height was then recorded to the nearest centimetre.

Weight was measured using SECA electric scales, which were calibrated with a 5Kg weight daily. Subjects were weighed without shoes or heavy outer garments and the weight recorded to the nearest 100g.

Body mass index (BMI) was calculated by dividing the weight in kg by the height in metres squared $(m)^2$.

2.6 Venous Blood Sampling

2.6.1. Natriuretic Peptide Concentrations

Venous blood was withdrawn after twenty minutes of supine rest into chilled tubes containing EDTA and trasylol (50 iu/ml). Samples were centrifuged at

3000rpm for 10 mins at 4 °C and the plasma separated and stored at -20 °C for subsequent analysis. Both N terminal atrial natriuretic peptide (N-ANP) and brain natriuretic peptide (BNP) concentrations were measured after extraction from plasma. The plasma was acidified with an equal volume of trifluoroacetic acid (TFA), mixed and centrifuged. The acidified plasma was allowed to pass slowly through a Sep-Pak C18 mini column (Waters) which had been preconditioned with methanol (5ml), then 1% TFA (5ml) and finally 1% TFA (2 X 3ml). The column was then washed with 1% TFA(5ml) followed by 0.1% TFA (2ml). The eluted peptides were dried by rotatory vacuum and redissolved in buffer for assay. Recoveries were 87% and 82% for N-ANP and BNP respectively.

N-ANP was measured, after dilution (1:100) by radioimmunoassay using an antibody from Peninsula Laboratories (RAS 9129) raised against the 1 to 30 N-terminal fragment. This antiserum has no detectable cross reaction with either C terminal ANP or BNP and has an IC_{50} of 18pg/tube in the assay. The within-assay and between-assay coefficients of variation (Cvs) for this assay were 15% (n=16) and 16% (n=48) respectively (Lang et al. 1993)

BNP was measured in the extract (1:4) using a radioimmunoassay kit for human BNP obtained from Peninsula Laboratories (RIK 9086). This has an IC_{50} of 20pg/tube. The within-assay and between-assay Cvs were 18% (n=16) and (n=46)15% respectively (Heublein et al. 1989).

2.6.2 The Angiotensin Converting Enzyme I/D Polymorphism

Lymphocytes were isolated from blood and DNA was prepared by standard techniques (by F Cambien at INSERM, Paris). The ACE I/D polymorphism was detected by polymerase chain reaction amplification (PCR), followed by allele specific hybridisation. Each amplification was performed using 500ng of DNA in a total volume of 50μl containing 25pmoles of primers (Rigat et al. 1992): 0.2U Taq polymerase (Euroentec), 200μM dNTP, 1X Taq buffer (10mM Tis-HCl pH9, 50mM potassium chloride, 1.5mM magnesium chloride, 0.2% TironX100 and 0.2mg/ml bovine serun albumin, 5% DMSO. After denaturation at 94°C for 1 min, 55°C for 1min, 72°C for 1 min and a terminal 72°C extension for 10 mins, genotyping was performed using allele-specific oligonucleotides (ASO)(Ludwig et al. 1993). One fifth of the PCR product was denatured in 150μl of 0.5M NaOH and 1.5M NaCl with 10μl of 0.05% bromophenol solution and blotted onto nylon membranes (N+ICN), neutralised with 0.2XSSC (standard saline citrate:0.15M NaCl and 0.015M trisodium citrate). Then the membranes were incubated in buffer (0.9 M NaCl, 0.09 M EDTA, 0.1% sodium dodecyl sulphate and 200μg sonicated DNA herring sperm) for 1 hour and hybridized at -5°C for 2 hours with 50 pmoles of allele-specific probes labelled with phosphorus-32. The membranes were washed twice at room temperature in 1XSSC for 5 mins, followed by 2 mins in 0.5XSSC at -3°C. The membranes were dried and autoradiography was carried out for 4-12 hours.

2.6.3 Serum Cholesterol

Venous blood was sampled for the measurement of non fasting serum total cholesterol, by an enzymatic method (Boehringer). Total serum cholesterol was recorded as the average of two measurements (mg/ml).

2.7 12 Lead Electrocardiogram

Standard 12 lead ECGs were coded by two observers, for the presence of pathological Q waves, left bundle branch block, ST segment depression, T wave abnormalities, left ventricular hypertrophy or atrial fibrillation/flutter using the Minnesota Coding system (codes; 1.1, 1.2, 1.3, 3.1, 3.3, 3.4, 4.1-4.4, 5.1-5.3, 7.1, 8.31, 8.32) (Prineas et al. 1982). Unresolved discrepancies were arbitrated by a third coder.

2.8 Alcohol Consumption

This was derived from the self reported questionnaire and expressed in units per week. Alcohol consumption beyond the 95th centile was defined as excessive.

2.9 Exercise Test

2.9.1 Conduct of the Test

Symptom limited, maximal exercise testing was carried out (on those subjects with no contraindication to treadmill stress testing, namely: unstable angina, recent myocardial infarction, decompensated chronic heart failure, critical aortic stenosis, severe hypertrophic cardiomyopathy, acute systemic illness, mechanical instability or a resting systolic blood pressure >220 mmHg or

>110 mmHg diastolic) using the Standardised Exponential Exercise Protocol (Northridge et al. 1990). A short demonstration was given by the technician prior to the test, the subject was then allowed to familiarise themselves with walking on the treadmill. All communication with the subject was standardised. Before commencing, it was explained that they should continue until they could go no longer. Encouragement was given every three minutes. A 12 lead ECG was recorded during the last 10 seconds of each minute of exercise and at 1, 3 and 5 minutes post exercise. Systolic blood pressure was measured every 3 minutes during exercise and immediately on stopping the test. Once a subject indicated their desire to stop, they were asked if they could manage a bit more, if they could not the test was then terminated. The test could also be stopped by the supervising physician (myself) if the subjects experienced grade III/IV chest pain, extreme dyspnoea or fatigue, leg pain, dizziness or light headedness, a significant arrhythmia (sustained ventricular tachycardia, rapid atrial fibrillation or supraventricular tachycardia), >3mm of ST segment depression, a fall in systolic blood pressure of >20mmHg, the development of a blood pressure>250/120 mmHg, ataxia, ST segment elevation of >1mm in a non-Q wave lead, decreasing heart rate or unwillingness on the part of the subject to continue (Froelicher, 1994).

Whether the test was subject or doctor limited, the reason for stopping was recorded and the duration of exercise noted.

2.9.2 Analysis of the Test

All exercise tests were analysed independently by two coders for the presence of ST segment depression. Discrepancies in coding were arbitrated by a third coder. The ST segment depression was assessed by measuring it in every lead of the resting and peak exercise ECGs using only the first codeable beat. If the peak exercise ECG was uncodeable then the first recovery ECG was used. The ST measurements were made using the Minnesota Coding Method (Prineas et al. 1982) at 80ms past the J point (determined using a graticule which allows the identification of the point and measurement of the ST segment without moving the line identifying the baseline). When two or more leads had the same ST change, the order of preference for using a lead was as follows: V5,V6, V4, V2,I,AvL,II,III,AvF,V1. The slope of the ST segment was also recorded using the Minnesota coding criteria as downward, horizontal or upward sloping. The rhythm at the beginning and end of the test was classified by the supervising doctor (myself). The analysis was carried out by experienced coders who had achieved a satisfactory standard in set tests of ECGs used as quality controls at various times during the WHO MONICA project.

2.10 Ethics

Ethics approval was obtained from the local Family Practitioner and Hospital Ethics Committees.

Chapter 3

The Prevalence of Symptomatic and Asymptomatic Left Ventricular Systolic Dysfunction in an Urban Population

3.1 INTRODUCTION

Despite the falling trend for other cardiovascular disorders, the incidence and prevalence of chronic heart failure (CHF) are predicted to rise substantially over the next ten years (Bonneaux et al. 1994). Already, increasing rates of hospitalisation for CHF have been reported from Europe and the United States (Gillum, 1987, McMurray et al. 1993, Ghali et al. 1990), and it now accounts for 1-2% of all health care expenditure (Costanzo et al. 1995).

In developed countries CHF is mainly attributable to left ventricular systolic dysfunction (although some patients with CHF have diastolic dysfunction). Its considerable morbidity and mortality (McKee et al. 1971, Ho et al. 1993b,The SOLVD Investigators, 1991) can be significantly improved by appropriate treatment (The SOLVD Investigators, 1991, Swedberg et al. 1987). Moreover, treatment of asymptomatic left ventricular systolic dysfunction can delay or prevent progression to symptomatic left ventricular systolic dysfunction and its consequences (The SOLVD Investigators, 1992, Pfeffer et al. 1992).

Despite the increasing importance of CHF and recent therapeutic developments, relatively little is known about its epidemiology and less still about its probable precursor, asymptomatic left ventricular systolic dysfunction. Most existing population surveys have relied upon a clinical diagnosis of CHF (McKee et al. 1971, Eriksson et al. 1989a, Schocken et al. 1992) However, recent work has shown that many symptomatic patients thought to have CHF do not have left ventricular systolic dysfunction, or, indeed any significant cardiac abnormality (Wheeldon et al. 1993b). In

addition, previous population surveys have been unable to identify those with asymptomatic left ventricular systolic dysfunction.

This chapter reports the first large scale epidemiological study, using two dimensional echocardiography, of the prevalence of both symptomatic and asymptomatic global left ventricular systolic dysfunction in men and women aged 25-74, randomly sampled from a geographically defined urban population.

3.2 METHODS

3.2.1 Population

This is as described in the methods section. It comprises 1640 individuals (response rate 83%). This present sample is representative of the parent cohort in all relevant criteria with the exception that the attendees were more affluent and there were fewer smokers. The prevalence of coronary heart disease and hypertension was the same as that of the parent cohort.

3.2.2 Echocardiogram

Standard 2D echocardiography was performed as described in the methods section: the left ventricular ejection fraction (LVEF) was obtained using the biplane disc summation method (Simpson's Rule) (Schiller et al. 1979), M-Mode parameters that were measured included the left ventricular end diastolic dimension (LVEDD) and fractional shortening (FS).

Quantitative echocardiogram analysis was carried out by a single observer. A random sample of 10% was reanalysed, blind to the first reading, by the

same observer and a separate 5% random sample analysed by a second observer. The intraobserver variation for the LVEF expressed as a median percentage error equalled 7%. The interobserver variation was 10%.

3.2.3 Definitions

Hypertension: a measured blood pressure of >160 mmHg systolic and/or 95 mmHg diastolic and/or current treatment with antihypertensive medication.

Ischaemic Heart Disease: the presence of either a self reported doctor diagnosis of angina and/or myocardial infarction and/or current use if nitrates and/or the presence of a Q wave indicative of previous myocardial infarction or major or minor ischaemia on the ECG (Minnesota codes: 6-1,6-2,6-3,6-8,8-3-1,8-3-2,4-1,4-2,4-3,4-4,5-1,5-2,5-3,1-3,7-1,1-1,1-2)

Left ventricular systolic dysfunction: to derive a "normal range" for LVEF, potentially abnormal subjects were defined as those with angina, myocardial infarction, hypertension, diabetes, a history of peripheral or cerebrovascular disease, those taking cardioactive medication and those with echocardiographic evidence of significant valvular heart disease. The distribution of LVEF was obtained for the remaining "normal" population. A LVEF≤30% was taken as "definite" left ventricular systolic dysfunction - a reduction of approximately one-third from the population mean. "Possible" left ventricular systolic dysfunction was defined as a LVEF≤35%.

Thus symptomatic left ventricular systolic dysfunction, or heart failure, refers to left ventricular systolic dysfunction with either the presence of "cardiac dyspnoea" from the MRC Breathlessness Questions (dyspnoea on effort, at rest or paroxysmal nocturnal dyspnoea in the absence of cough and sputum

production for more than three days of the week for three months of the year) and/or current therapy with a loop diuretic. Asymptomatic left ventricular systolic dysfunction denotes left ventricular systolic dysfunction in the absence of cardiac dyspnoea or loop diuretic therapy.

3.2.4 Statistical Analysis

Chi squared tests were used to evaluate differences in the proportions of individuals with and without left ventricular systolic dysfunction. Continuous variables between those in whom an echocardiographic LVEF was obtainable versus those in whom it was unobtainable were compared using the Student's t test. Linear regression analysis (MINITAB) was used to determine the effect of the LVEF on the presence of symptoms (i.e. breathlessness or the requirement of a loop diuretic). The other variables included in the model were age, smoking, BMI, IHD, and hypertension.

3.3 RESULTS

3.3.1 Echocardiogram Acceptability

A biplane ejection fraction was measurable in 89.5% (1467) of the subjects, ranging from 85.6% in men aged 65-74 to 95.8% in women aged 35-44. (Table 3.1).

This measurement was fairly uniformly obtainable across the age sex groups (although the measurement was statistically significantly more obtainable in younger subjects, p=0.002) when compared to the more commonly used M-

Mode parameters of LV function, which were only available in 68.5% of subjects (see Table 3.2). The ability to perform M-Mode analysis declined with markedly with age ($p<0.0001$), partly reflecting poorer preservation of the parasternal echo window and also deformation of the basal portion of the interventricular septum (Table 3.2).

Due to the greater efficacy of the Biplane Simpson's Rule LVEF in evaluating LV function for all ages within our population, as well the evidence that it yields the best correlation with other modalities used to assess left ventricular ejection fraction such as radionuclide ventriculography and angiography, we have used this measurement as our gold standard for LV function (Stamm et al 1992). All subsequent analyses of LV function refer to this gold standard.

Subjects in whom a LVEF could be measured were significantly younger, had a lower prevalence of diabetes and hypertension and had lower body mass indices. There was also a trend toward them having a lesser prevalence of angina (Table 3.3).

3.3.2 Left Ventricular Ejection Fraction

LVEF was skewed to the left in the total population in whom an adequate echo examination was available (n=1467), and had a mean value of 46.6% (Figure 3.1). LVEF was approximately normally distributed in the "normal" population free of cardiovascular disease (Figure 3.2) with a mean value of

Table 3.1

Left Ventricular Ejection Fraction (Simpson's Rule) Obtainability

Age group (yrs)	**Male** (n)	**Female** (n)
25-34	95.3% (122)	95.4% (126)
35-44	88.2% (135)	95.8% (162)
45-54	85.7% (138)	86.9% (159)
55-64	90.8% (158)	86.6% (149)
65-74	85.6% (155)	87.2% (164)

Table 3.2

LVEDD and FS Obtainability.

Age group (yrs)	**Male** % (n)	**Female** (n)
25-34	87.0% (111)	93.7% (124)
35-44	81.8% (125)	83.6% (141)
45-54	60.3% (97)	67.9% (124)
55-64	62.4% (108)	54.5% (149)
66-74	49.7% (90)	46.5% (87.4)

Table 3.3

Comparison of Characteristics of Those in Whom a LVEF Could be Measured Compared to Those in Whom it Was Unavailable

		LVEF (n=1467)	No LVEF (n=173)	P value
Age	mean (SD) range	50.4(14) 25-74	54(12) 25-74	0.0002
Sex	males	48.1%	51.4%	0.42
Angina		10.6%	15.6%	0.05
Self reported MI		5.1%	7.2%	0.26
Diabetes		2.5%	6.4%	0.004
Hypertension		38.6%	50.3%	0.004
SBP(mmHg)	mean(SD)	132(23)	137(23)	0.67
DBP(mmHg)	mean(SD)	78(12)	80(12)	0.86
Body Mass Index (kg/m^2)	mean(SD)	25.9(4.3)	29.4(7.6)	<0.0001
Total Cholesterol (mg/ml)	mean(SD)	6.07 (1.24)	6.06 (1.17)	0.35

Figure 3.1 ***Frequency Distribution of Left Ventricular Ejection Fraction in the Total Population***

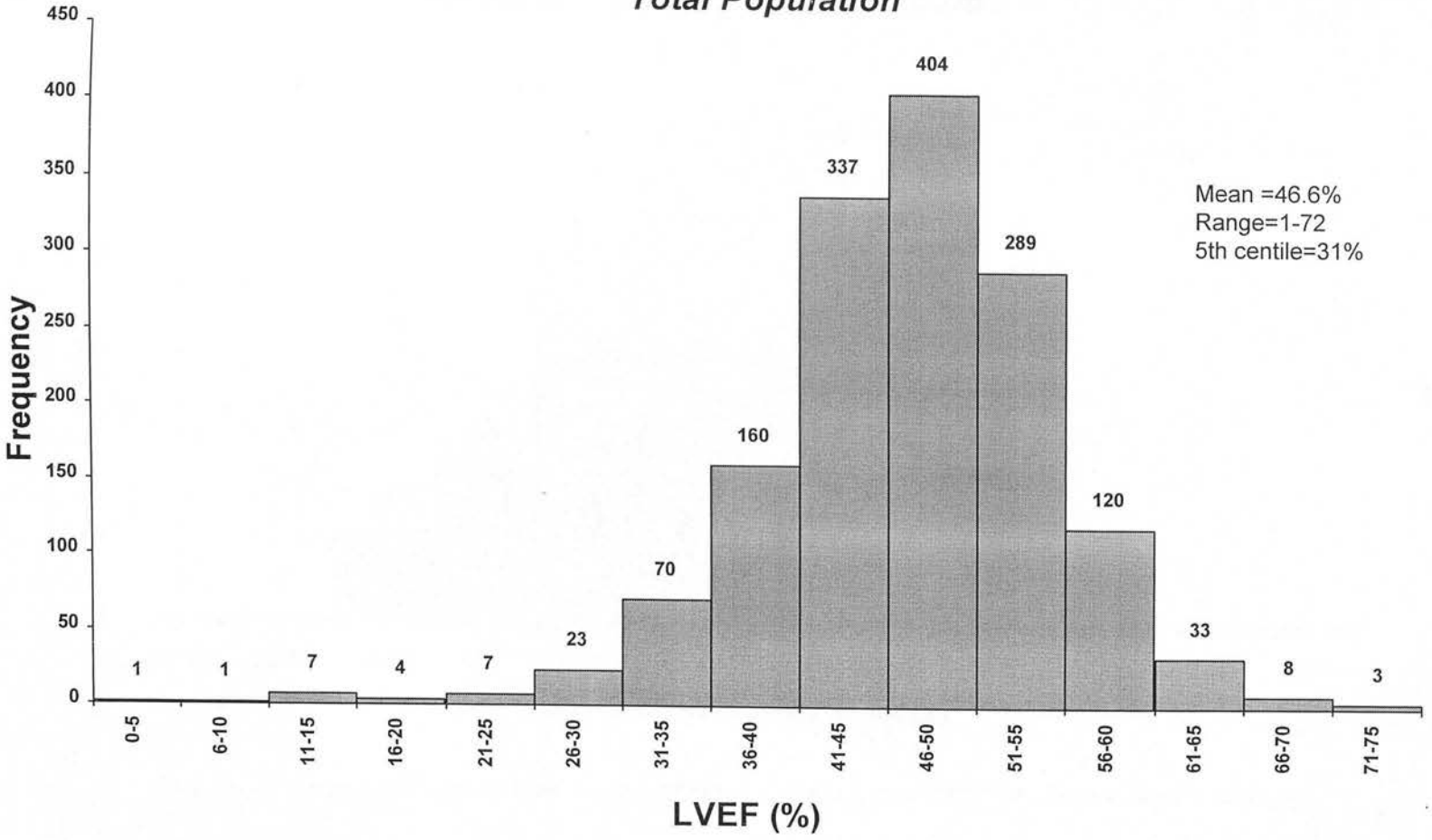
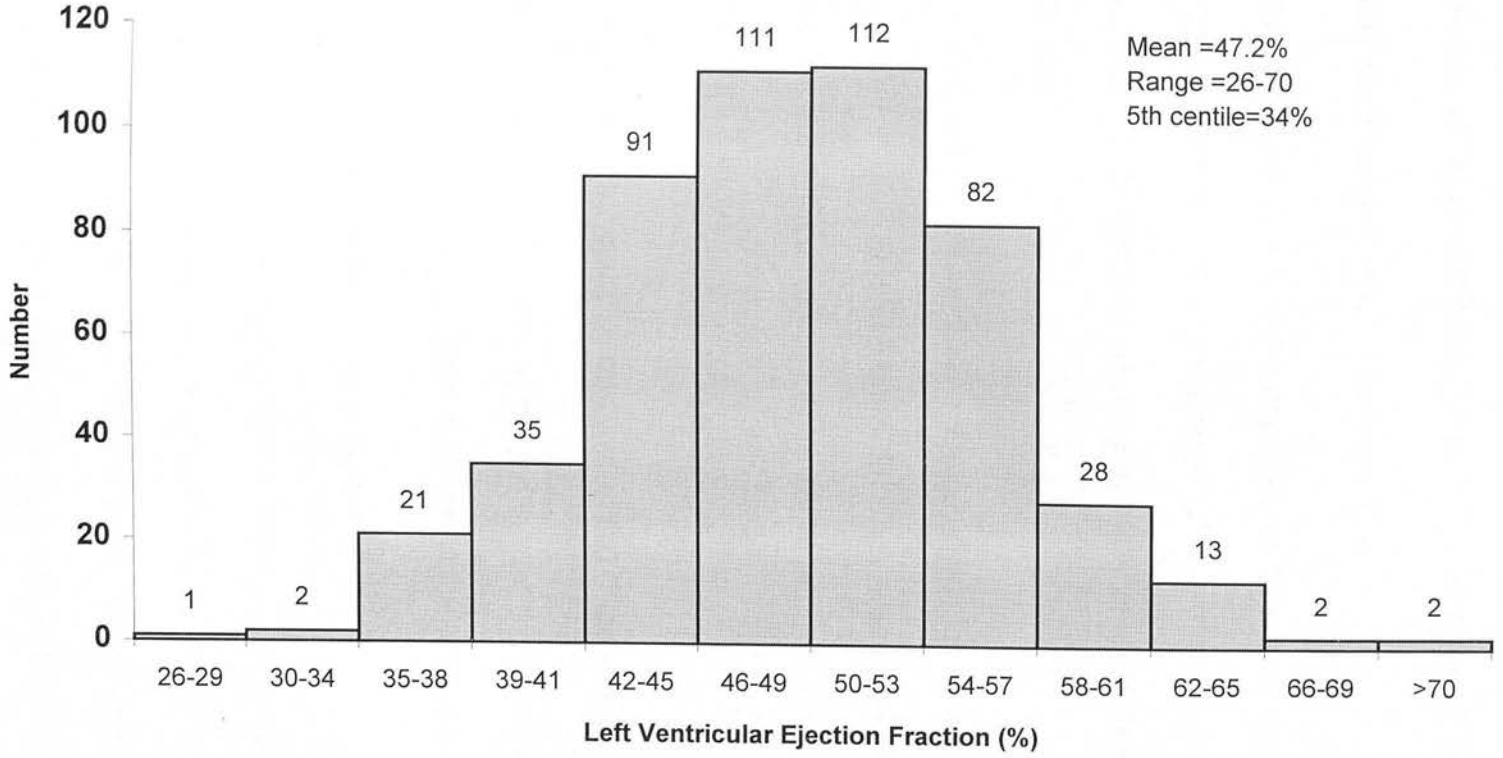


Figure 3.2 :Frequency Distribution of Left Ventricular Ejection Fraction in the "Normal" Population



Legend : Frequency distribution of Left Ventricular Ejection Fraction in subjects free of cardiovascular disease

47.3% (standard deviation 6.5, range 26-70). Two standard deviations below the mean was 34% and the 5th centile value was 35%. The mean left ventricular ejection fraction was slightly less in "normal" men (46.6% SD 6.6) than in women (48% SD 6.4%) (p=0.02).

3.3.3. Prevalence of Left Ventricular Systolic Dysfunction (Figure 3.3)

'Definite' (left ventricular ejection fraction ≤30%)

This was present in 2.9% (n=43) of the population with a marked difference in the prevalence between men (4%) and women (2%) (p<0.001). Symptomatic left ventricular systolic dysfunction occurred in 1.4% of subjects while 1.5% were asymptomatic.

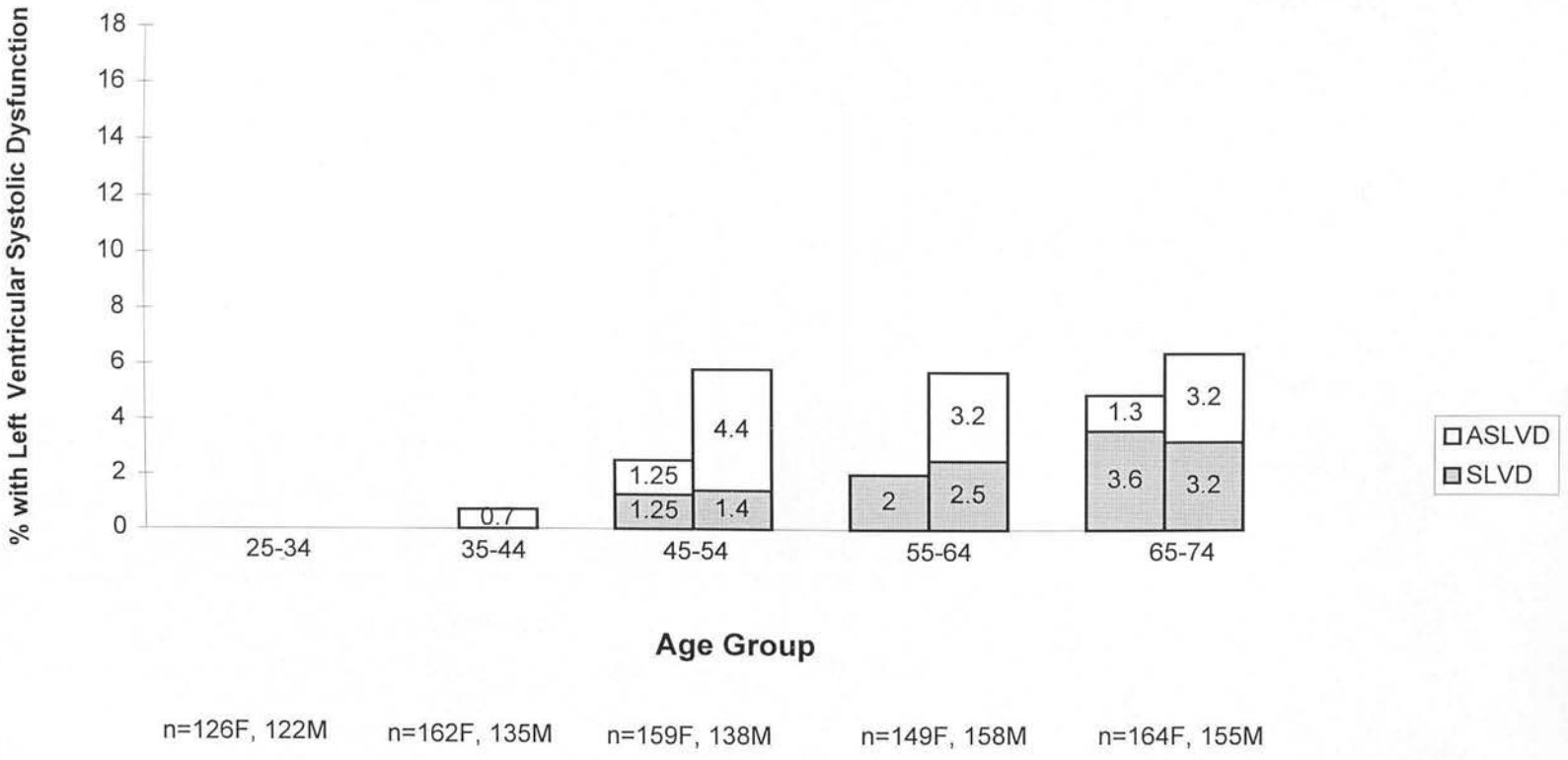
The prevalence of definite left ventricular systolic dysfunction increased with age and was higher in men than in women for each age group (Figure 3.3), ranging from 0.0% in men and women aged 25-34 yrs to 6.4% in men over age 65 years (Figure 3.3).

'Possible' (left ventricular ejection fraction ≤35%) (Figure 3.4)

The prevalence of an ejection fraction of ≤35% was higher in males and increased with age. Overall 7.7% (113) of subjects had an ejection fraction ≤35%, of whom 77% were asymptomatic (Figure 3.4).

The proportion of symptomatic subjects does increase as the ejection fraction gets lower (see Table 3.4). In the linear regression model the presence of left ventricular systolic dysfunction was independently associated with the presence of symptoms (p=0.02). Other variables independently associated

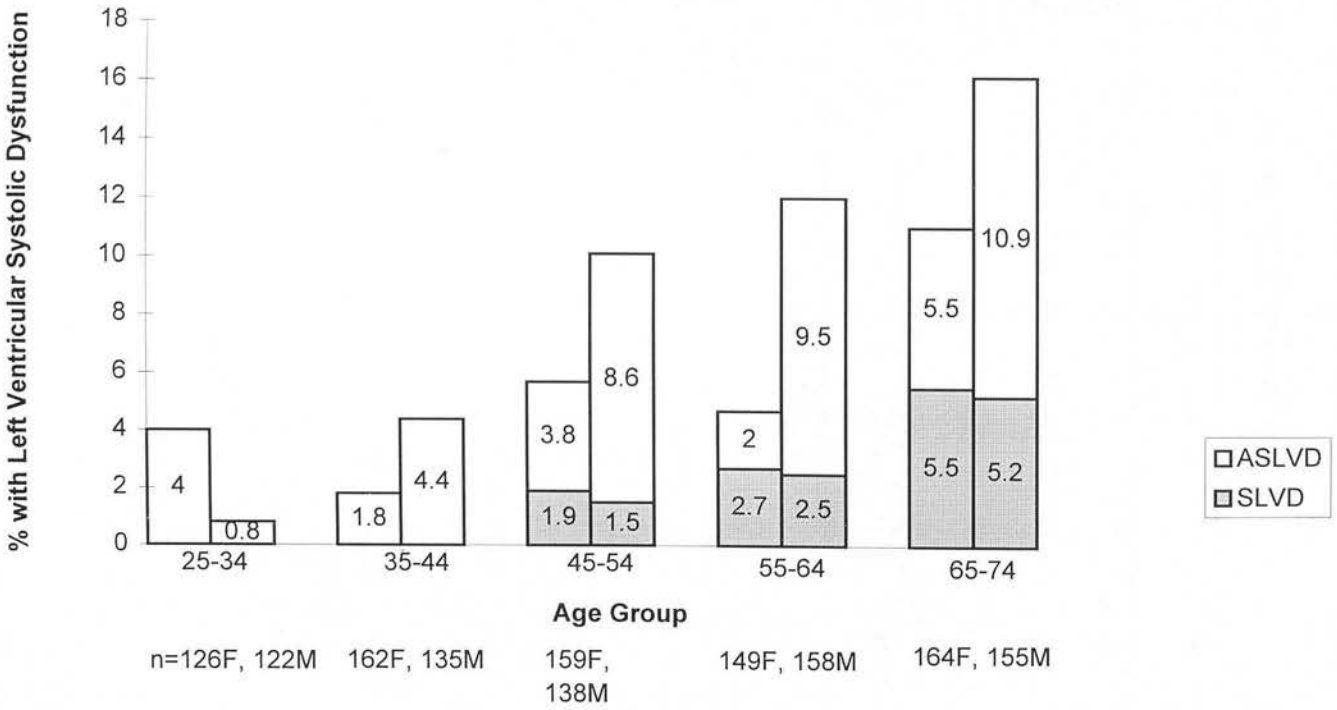
Figure 3.3 : Prevalence of a Left Ventricular Ejection Fraction <=30%



Legend to Figure 3.3

ASLVD is asymptomatic left ventricular systolic dysfunction, SLVD represents symptomatic left ventricular systolic dysfunction. The denominators in each age group are displayed underneath the graph, F denotes females and M, males.

Figure 3.4 : Prevalence of a Left Ventricular Ejection Fraction <=35%



Legend to Figure 3.4

ASLVD is asymptomatic left ventricular systolic dysfunction, SLVD represents symptomatic left ventricular systolic dysfunction. The denominators in each age group are displayed underneath the graph, F denotes females and M males.

Table 3.4

Symptomatic and Asymptomatic Left Ventricular Systolic Dysfunction by Ejection Fraction

Ejection fraction %	Number symptomatic	Number asymptomatic	Total	Proportion symptomatic
≤20	8	4	12	67%
21-25	3	4	7	43%
26-30	9	13	22	41%
31-35	6	61	67	7%
≥36	146	1168	1314	11%

with breathlessness or the need for loop diuretic therapy were increasing BMI ($p<0.001$), the presence of IHD ($p<0.001$) and hypertension ($p=0.03$). Current smoking ($p=0.97$) and age (0.054) were not significant in the model. One hundred percent of those with symptomatic left ventricular systolic dysfunction and 95% of those with asymptomatic left ventricular systolic dysfunction had some evidence of IHD or hypertension. Using a cut-point for left ventricular ejection fraction of ≤35%, 75% have IHD or hypertension.

3.3.4 Treatment and Left Ventricular Systolic Dysfunction

Of symptomatic subjects with definite left ventricular systolic dysfunction, 65% (11) were receiving treatment with a diuretic and/or an angiotensin converting enzyme inhibitor and/or digoxin.

In subjects with a LVEF≤30% (irrespective of their symptom status): 18% (7/39) were currently taking an ACE inhibitor, 31% (4/13) of those with symptomatic definite left ventricular systolic dysfunction and 11.5% (3/26) with asymptomatic left ventricular systolic dysfunction were on ACE inhibitor therapy.

5.4 DISCUSSION

This is the first study to my knowledge to report the prevalence of both symptomatic and asymptomatic left ventricular systolic dysfunction in a geographical population of men and women using an objective measure of left ventricular function.

The study demonstrates that a low ejection fraction is common, with 2.9% of the population having definite left ventricular systolic dysfunction, of which half is asymptomatic.

Given that left ventricular ejection fraction is normally distributed, the first question raised by this work is "What is normal left ventricular function?". The decision to choose ≤30% to indicate 'definite' left ventricular systolic dysfunction is justified by 100 % of those with symptomatic left ventricular systolic dysfunction and 95% of those with asymptomatic left ventricular systolic dysfunction having a plausible underlying cause, i.e. IHD or hypertension. However, a 2.9% prevalence of definite left ventricular systolic dysfunction should be regarded as a minimum. Using a cut-point for left ventricular ejection fraction of ≤35%, the prevalence of left ventricular systolic dysfunction increases to 7.7%, and, of these subjects, 75% have IHD or hypertension. However, 35%, which is on the borderline of statistical normality for this measurement, would include biologically normal subjects. Therefore, in order to define a minimum prevalence which also takes account of the variability of echocardiographic left ventricular ejection fraction, I have opted for a value where there can be little doubt about its clinical significance. The true prevalence of left ventricular systolic dysfunction will, however, lie somewhere between 2.9% and 7.7%.

It is also evident from the population sample that the amount of left ventricular systolic dysfunction may have been underestimated as attendees were more affluent and less likely to be smokers, and those in whom a left ventricular

ejection fraction could be measured were younger, had a lower prevalence of hypertension and a displayed a trend towards less ischaemic heart disease.

Using a definition of CHF as "symptomatic left ventricular systolic dysfunction" (Task Force on Heart Failure of the European Society of Cardiology 1995) facilitates comparison with other studies. In this population, 1.4% had symptomatic left ventricular systolic dysfunction. "The study of men born in 1913" (Eriksson et al. 1989) which was limited to men, with CHF diagnosed on symptoms and signs, quoted "manifest heart failure" as occurring in 2.4% at 54 years, 4.3% at 60 years and 13% at 67 years. The results presented here yielded slightly lower prevalence rates for symptomatic left ventricular systolic dysfunction of 1.5% in men aged 45-54, 2.5% in those aged 55-64 and 3.2% in those aged 65-74. This may be due to the power of the present study in distinguishing subjects, diagnosed clinically, as having CHF who have normal systolic function. It should also be borne in mind that this cut off value for left ventricular systolic dysfunction is a strict one and gives a minimum estimate.

The prevalence of symptomatic definite left ventricular systolic dysfunction is close to that of the recent NHANES Survey (Schocken et al. 1992) quoting 2% for the general US population and to that in a recent community study from a UK city similar to Glasgow (Mair et al. 1996). These rates are higher than previously reported in the Framingham study (McKee et al. 1971) where more advanced stages of the disease may have been detected due to stricter diagnostic criteria. The Framingham Study also began in 1949 and the prevalence of CHF is rising (Gillum, 1987, McMurray et al. 1993, Ghali et al.

1990), which may partly explain the higher prevalence. Alternatively, North Glasgow is an area with a high prevalence of IHD, and is, therefore, likely to have more CHF. These results confirm that CHF is significantly more common in men than women (McKee et al. 1971). The prevalence reported is also greater than that detected in studies based on prescription data which clearly pick up a more advanced stage of the disease after it has crossed the threshold for therapeutic intervention (Gibson et al. 1966, Parameshwar et al. 1992b, Clarke et al. 1995)

Perhaps the most important novel finding of this work is that asymptomatic left ventricular systolic dysfunction is at least as common as CHF. The Framingham Group found a reduced fractional shortening in 5.2% of men and 1.9% of women from their "Offspring Cohort" (Vasan et al. 1997a). Comparisons are difficult as no assessment of global LV function using a biplane method was carried out in that study. In this study 2.7% of asymptomatic men and 0.6% of asymptomatic women had definite left ventricular systolic dysfunction. Nevertheless, it should be reiterated that this is a minimum prevalence since 8.9% of asymptomatic males and 4.2% of asymptomatic females had an ejection fraction ≤35%. Gardin et al, have also published work on subjects over 65 years, using a subjective assessment of left ventricular function, and found it to be reduced in 6.8% of asymptomatic men and 1.8% of women (Gardin et al. 1995). The present study's figures are similar with 4.3% and 2% of asymptomatic men and women, respectively, having definite evidence of left ventricular systolic dysfunction. However if we were to look at those with a left ventricular ejection fraction ≤35%, this study

has much higher estimates with 14.6% of asymptomatic men and 8.9% of asymptomatic women over 65 years having an ejection fraction below this level.

Interestingly, the proportion of left ventricular systolic dysfunction which is asymptomatic is significantly greater in the younger age groups. One explanation is that asymptomatic left ventricular systolic dysfunction is, indeed, a latent precursor phase which progresses to CHF with increasing age due to intrinsic progress of left ventricular systolic dysfunction or to further cardiovascular events. It is also interesting to note that the proportion of left ventricular systolic dysfunction that is symptomatic increases as the ejection fraction falls. This also lends weight to the asymptomatic phase being a transitory harbinger of more serious disease.

Whether the asymptomatic left ventricular systolic dysfunction detected in this work will progress to CHF is as yet unknown but will be resolved at subsequent follow up. That some subsets with asymptomatic left ventricular systolic dysfunction will progress is supported by work indicating a higher odds ratio for the development of cardiovascular disease for those with subclinical LV dilation (Lauer et al. 1992) in the Framingham Offspring Cohort and in those with asymptomatic left ventricular systolic dysfunction in the SOLVD Prevention Trial (The SOLVD Investigators, 1992). Additionally, the increased hazard ratio for the development of CHF obtained in the 11 year follow up of subjects with subclinical left ventricular dilation in the Framingham Offspring Cohort (Vasan et al. 1997a) suggests that the asymptomatic left ventricular systolic dysfunction we have uncovered will also progress to CHF.

Echocardiography proved a useful epidemiological tool in this work; the left ventricular ejection fraction according to Simpson's Rule was readily obtained in nearly ninety percent of our subjects, making it more useful than M-Mode (only adequately obtained in 68.5%).

However, comparisons between studies using echocardiography pose some difficulties because differences in hardware, software and quantitative analysis techniques will cause unquantifiable differences.

As just over half of the left ventricular systolic dysfunction identified in this study was asymptomatic and the symptomatic left ventricular systolic dysfunction was undertreated, and since progression of asymptomatic left ventricular systolic dysfunction to CHF can be ameliorated by the use of ACE inhibitors in patients with cardiac disease, (The SOLVD Investigators, 1992) these findings have important implications both for prevention and screening for left ventricular systolic dysfunction.

This chapter has demonstrated that left ventricular systolic dysfunction is more common than some diseases such as breast and cervical cancer (with a similar prognosis) for which considerable resources for screening are deployed. Ideally requirements for health care should be estimated using disease prevalence figures calculated from accurate, objective techniques and applying them to future estimations of an ageing population. If the current patterns of health care persist for CHF then the implication is that substantially more resources will be required. Nearly twenty per cent of patients with CHF are hospitalised at least once per annum (Bourassa et al. 1993). In-patient treatment of CHF costs the NHS £214.25 million per annum

(59.5% of the total direct costs to the NHS for CHF) (McMurray and Davie, 1996).

Policy makers need to devise ways of reducing the potentially increasing burden of left ventricular systolic dysfunction on resources. Effective drug therapy for symptomatic left ventricular systolic dysfunction reduces mortality, hospitalisation rates and length of stay (The SOLVD Investigators, 1991). Optimising the use of appropriate drug therapy should be a priority for health care purchasers considering that only 31% of those with symptomatic left ventricular systolic dysfunction were on desirable CHF therapy. In addition, the use of ACE inhibitors has been shown to be cost effective. Also alarming, but perhaps less surprising, is the finding that only 11.5% of subjects with asymptomatic left ventricular systolic dysfunction were on effective treatment.

This chapter, by revealing its magnitude, has highlighted the need to focus on case finding for symptomatic, and screening for asymptomatic left ventricular systolic dysfunction. The next concentrates on the high risk groups in which they reside.

Chapter 4

The Correlates of Left Ventricular Systolic Dysfunction in an Urban Population

4.1 INTRODUCTION

When the Framingham Heart Study reported its findings, over a quarter of a century ago, three quarters of all the CHF they identified was attributed to hypertension (McKee et al. 1971). Similarly in the "Study of the men born in 1913", hypertension was implicated as a significant aetiological factor in over half the cases they discovered (Eriksson et al. 1989). More recently, data from the heart failure treatment trials has indicated that ischaemic heart disease is now the principal cause of CHF; being responsible for approximately three quarters of cases (The SOLVD Investigators. 1991).

Since the main population-based studies on CHF reported, there appears to have been a shift in the main aetiology of CHF, from hypertension to ischaemia. This observation, coupled with the fact that there are no epidemiological data on the determinants of left ventricular systolic dysfunction in the general population, showed a need to update this information. This chapter, therefore, examines the aetiological correlates of left ventricular systolic dysfunction in a random sample of men and women aged 25-74 in a geographical population with a high standardised mortality ratio for coronary heart disease.

4.2 METHODS

4.2.1 Population

For this section of the study the population is as described in the methods and consists of the 1467 subjects who had a biplane ejection fraction available. They also had questionnaire data regarding their history of

myocardial infarction, angina and diabetes, and their current drug treatment, a measurable systolic and diastolic blood pressure and a 12 lead ECG, which was Minnesota Coded.

4.2.2 Definitions

Angina: a history of physician diagnosed angina and/or the current use of nitrate drugs.

Myocardial infarction (MI): a history of doctor diagnosed MI or the presence of a pathological Q wave on the ECG.

ECG Ischaemia: Any of the following Minnesota Codes including (1) Minor Ischaemia (6-1,6-2, 6-3, 6-8, 8-3-1, 8-3-2) (2) Major Ischaemia (4-1, 4-2, 4-3, 4-4, 5-1, 5-2, 5-3, 1-3 and 7-1) and (3) MI (1-1 or 1-2).

Ischaemic Heart Disease (IHD): the presence of angina and/or MI and/or ECG ischaemia.

ECG abnormal: Any code including ECG ischaemia plus left ventricular hypertrophy (code 3-1 and 3-3) and/or left bundle branch block (7- codes).

Left Ventricular Hypertrophy (LVH): refers to ECG criteria for LVH (Minnesota codes 3-1 and/or 3-3).

Hypertension: a measured blood pressure of >160 mmHg systolic and/or 95 mmHg diastolic and/or current treatment with antihypertensive medication.

Diabetes mellitus: a history of diabetes and/or current treatment with an oral hypoglycaemic agent or insulin.

Definite left ventricular systolic dysfunction: A left ventricular ejection fraction $\leq 30\%$.

Possible left ventricular systolic dysfunction: A left ventricular ejection fraction≤35%.

Regarding left ventricular systolic dysfunction, symptomatic refers to the presence of "cardiac dyspnoea" and/or current therapy with a loop diuretic and asymptomatic, the absence of cardiac dyspnoea or loop diuretic therapy. (see Methods for fuller explanations, where the definitions of alcohol excess and valvular abnormalities are also given).

4.2.3 Statistical Analysis

Chi Square or Fisher's Exact tests (where appropriate) were used to evaluate differences in the proportions of individuals with risk factors between the subgroups of the study population. Odds ratios were estimated using linear logistic regression analysis. A p value of <0.05 has been considered significant.

4.3 RESULTS

4.3.1 Correlates of Left ventricular systolic dysfunction (Table 4.1)

Ischaemic Heart Disease

Table 4.1 shows the prevalence of various manifestations of ischaemic heart disease (IHD) in symptomatic and asymptomatic individuals with definite left ventricular systolic dysfunction, compared with symptomatic and

Table 4.1: Risk Factors for Left Ventricular Systolic Dysfunction in Symptomatic and Asymptomatic Subjects with and Without Left Ventricular Systolic Dysfunction.

Risk Factor	Symptomatic LVSD	Symptomatic No LVSD	Odds Ratio [95% CI]	p*	Asymptomatic LVSD	Asymptomatic No LVSD.	Odds Ratio [95%CI]	p$^{\psi}$
Ischaemic Heart Disease	95% (21)	43% (197)	25[3.6,100]	<0.001	71% (21)	17%(1138)	12.5[4.5,33.3]	<0.001
Angina	62% (21)	26% (206)	4.5[1.8,11.1]	<0.001	43% (21)	6% (1155)	11.1[4.5,25]	<0.001
MI	50% (22)	15% (210)	5.9[2.3,14.3]	<0.001	14% (21)	2% (1167)	6.7[1.8,25]	0.02
ECG ischaemia	77% (22)	25% (201)	10[3.6,33.3]	<0.001	50% (20)	13% (1151)	6.7[2.8,16.7]	<0.001
Hypertension	68% (22)	51% (211)	2.1[0.8,5.3]	0.12	52% (21)	17% (1166)	5.3[2.2,12.5]	<0.001
ECG abnormal	77% (22)	8% (201)	9.1[3.1,25]	<0.001	60% (20)	18%(1151)	7.1[2.8,16.7]	<0.001
Left Ventricular Hypertrophy	14% (22)	9%(201)	1.6[0.4,5.9]	0.44	15%(20)	6%(1151)	2.8[0.8,10]	0.12
Alcohol excess	0% (14)	3% (145)	*not calculated	0.87	14% (14)	5%(898)	0.3[0.1,1.5]	0.17
Valvular abnormality	25% (12)	6%(194)	5.5[1.3,25]	<0.001	0% (14)	4%(1093)	*not calculated	0.99

Legend to Table 4.1:

LVSD is definite left ventricular systolic dysfunction. Ischaemic heart disease is a history of angina or infarction or ECG evidence of ischaemia or infarction or the use of nitrates. Hypertension refers to a history of hypertension, a measured blood pressure of >160 mmHg systolic or 95 mm Hg diastolic or the current use of anti-hypertensive medication. Left ventricular hypertrophy refers to electrocardiographic evidence of hypertrophy.

* zero cell

p* refers to the p value for Chi Square tests between those with symptomatic LVSD compared to those with a LVEF>30% who were symptomatic. p^{Ψ} refers to p values for asymptomatic LVSD versus asymptomatic subjects without LVSD.

The percentage of those with the risk factors in each subgroup is quoted. The number in parenthesis is the absolute number of subjects in each subgroup with the given risk factor or abnormality.

asymptomatic subjects with ejection fractions >30%. Some evidence of IHD (i.e. a history of angina, myocardial infarction or electrocardiographic evidence of ischaemia or infarction: Q waves, left bundle branch block or ST/T wave change) was present in 95% of those with symptomatic left ventricular systolic dysfunction and 71% of those with asymptomatic left ventricular systolic dysfunction (p=0.04). Fifty percent of those with symptomatic left ventricular systolic dysfunction reported a prior myocardial infarction and 62% had angina (self-reported or current use of nitrates). Of those with asymptomatic left ventricular systolic dysfunction, only 14% had a history of myocardial infarction. However, 43% of them had a history of angina (p=0.01 for prior myocardial infarction, p=0.02 for angina - symptomatic left ventricular systolic dysfunction *versus* asymptomatic left ventricular systolic dysfunction).

IHD unaccompanied by hypertension occurred in one third of those with symptomatic left ventricular systolic dysfunction *versus* 17% of symptomatic individuals with ejection fractions >30% (p<0.001) and also in one third of those with asymptomatic left ventricular systolic dysfunction compared to 11% of asymptomatic subjects with ejection fractions >30% (p<0.001).

In subjects with a history or electrocardiographic evidence of myocardial infarction, 21% had an ejection fraction ≤35% and in 15%, it was ≤30%. Of those with angina, 11% had an ejection fraction ≤35% and 7% had definite left ventricular systolic dysfunction.

In a univariate analysis, a history of myocardial infarction was associated with an odds ratio of 10.8 (95% CI: 5.4, 21.5:p<0.001) for left ventricular systolic

dysfunction, angina resulted in an odds ratio of 10.7 (95% CI: 5.1, 20.1: p<0.0001) and electrocardiographic evidence of ischaemia or infarction gave an odds ratio of 10.4 (95% CI: 5.5,20.0: p<0.001) for left ventricular systolic dysfunction.

Seventy seven percent of those with symptomatic left ventricular systolic dysfunction and 60% of those with asymptomatic left ventricular systolic dysfunction had an electrocardiogram abnormality (defined as: Q wave, left bundle branch block, ST/T change, left ventricular hypertrophy, atrial fibrillation/flutter) compared to 8% (symptomatic) and 18% (asymptomatic) of those with normal left ventricular function (p<0.001).

Hypertension

Table 4.1 also gives the prevalence of hypertension in subjects with symptomatic left ventricular systolic dysfunction and asymptomatic left ventricular systolic dysfunction compared to symptomatic and asymptomatic individuals with a left ventricular ejection fraction >30%. Some evidence of hypertension (history, measured or treated) was found in 68% of those with symptomatic left ventricular systolic dysfunction compared with 51% of symptomatic subjects without left ventricular systolic dysfunction. Those with asymptomatic left ventricular systolic dysfunction had a prevalence of hypertension of 52% compared to 17% in asymptomatic subjects with normal left ventricular function (p<0.001).

In the univariate analysis the presence of hypertension was associated with an odds ratio of 5.2 for left ventricular systolic dysfunction (95% CI: 2.8, 9.7:

p<0.001). Evidence of left ventricular hypertrophy on the electrocardiogram was more common in those with left ventricular systolic dysfunction but not significantly so: odds ratio 2.4 (95% CI: 1.0, 5.9: p=0.08).

The presence of hypertension and IHD are individually associated with an increased risk of left ventricular systolic dysfunction in both symptomatic and asymptomatic subjects. When considered jointly in a logistic regression analysis, both were predictive of left ventricular systolic dysfunction, conditional odds ratios (95% CI) were 14.3(6.1, 33.4) and 2.5(1.3, 4.8) for IHD and hypertension respectively. These calculations were carried out for symptomatic and asymptomatic subjects together so that adequate numbers were available for the analysis.

In a more detailed multivariate stepwise logistic regression analysis the independent useful predictors of left ventricular systolic dysfunction (odds ratios [95% CI] were angina (5.1[2.6,33.4]), electrocardiographic evidence of ischaemia or infarction (5.9 [2.9, 12.0]), hypertension (3.0[1.5,5.9]) and male sex (2.1[1.1,4.3]).

In subjects with left ventricular ejection fractions ≤35%, 75% had evidence of IHD and/or hypertension.

Hypertension: The Effect of Different Degrees of High Blood Pressure.

Table 4.2 depicts the prevalence of left ventricular systolic dysfunction, and mean LVEF according to the severity of hypertension. The blood pressure groups are Stage 1 a blood pressure of <140 mmHg systolic and <90 mmHg

Table 4.2 ***The Effect of Increasing Levels of Hypertension on the Prevalence of Left Ventricular Systolic Dysfunction***

Stage of BP	Prevalence of LVSD (n)	Odds Ratio (95%CI)	Mean LVEF % (SD)	Number in Stage
1	1.4%(12)	1	47.1(7.6)	911
2	3.1%(9)	2.2(0.9,5.2)	45.8(7.7)	292
3	5.8%(23)	6.7(3.3, 13.6)	45.4(10)	238

Legend to Table 4.2: LVSD denotes left ventricular systolic dysfunction. The number in parenthesis is the actual number with the risk factor. Stage 1 refers to normotension i.e a SBP<140 mmHg and a DBP<90mmHg. Stage 2 denotes a SBP≥140 mmHg and ≤159 mmHg and/or a DBP ≥90 mmHG and ≤94 mmHG. Stage 3 is either a SBP≥160 mmHg and/or a DBP≥95 mmHG. The proportions of subjects with LVSD were significantly different between stages 1 and 3 ($p<0.001$) and stages 2 and 3 ($p=0.004$), the difference between stages 1 and 2 was not statistically significantly different ($p=0.07$) on Chi Squared analysis. The mean LVEF between stages 1 and 3 ($p=0.02$) was significantly different whereas that between stages 1 and 2 ($p=0.06$) and stages 2 and 3 was not ($p=1$). (Student's t tests).

diastolic, Stage 2 a systolic BP >140 and <=159 and or a diastolic BP of >90 mmHg and or <=94 mmHg, Stage 3 denotes a systolic blood pressure of ≥160 mmHg and/or a diastolic of ≥95 mmHg (these stages are irrespective of whether the subject was taking antihypertensive drugs as there was no significant difference either in the mean LVEF or the proportion with left ventricular systolic dysfunction between those within each stage whether they taking or not taking antihypertensive medication; see Table 4.3). The odds ratio (95% confidence intervals in parentheses) for a blood pressure of ≥140 and ≤159 mmHg systolic and/or ≥90 mmHG and ≤94 mmHg diastolic being associated with left ventricular systolic dysfunction was 2.2 (0.9, 5.2) where as this increased to 6.7 when the blood pressure was ≥160 mmHg systolic and/or ≥95 mmHG diastolic (p=0.004 Chi Square).

Diabetes mellitus

The prevalence of left ventricular systolic dysfunction was highest in diabetics: in whom 29% (14/48) had a LVEF≤35% and 17%(8/48) ≤30%. Three-quarters of definite left ventricular systolic dysfunction in diabetics was attributable to IHD (6/8 with evidence of a previous myocardial infarction, in whom 3/6 had coexisting hypertension), the remaining quarter (2/8) were hypertensive without evidence of IHD.

Other causes of left ventricular systolic dysfunction

Significant valvular heart disease on the echocardiogram and alcohol consumption beyond the 95th centile value for the population studied were not more prevalent in those with left ventricular systolic dysfunction.

Table 4.3: The Degree of Hypertension and the Prevalence of Left Ventricular Systolic Dysfunction

Stage	Prevalence of LVSD % (n)	Mean LVEF (SD)	Number
1	1.2% (11)	47.1 (7.4)	855
1a	4.7% (2)	46.7 (9.4)	56
2	2.1% (6)	46.0 (7.5)	247
2a	7.0% (3)	44.9 (8.9)	45
3	7.6% (18)	44.9 (10.2)	186
3a	7.0% (3)	47.6 (9.1)	52

Legend to Table 4.3: LVSD represents left ventricular systolic dysfunction. The stages are as for Table 2, except that the presence of an **a** denotes the presence of antihypertensive medication. The number in parenthesis is the absolute number of subjects with that risk factor.

The differences between the mean LVEF values between stages 1 and 1a ($p=1$), 2 and 2a ($p=1$), and 3 and 3a ($p=0.5$) failed to achieve statistical significance (Student's t tests). Similarly, the proportions with LVSD between stages 1 and 1a ($p=0.16$), 2 and 2a ($p=0.13$), 3 and 3a ($p=0.38$) were not significant (Chi-Squared analysis.)

4.4 DISCUSSION

The first point this chapter demonstrates is that both ischaemic heart disease and hypertension were extremely prevalent in this population and often co-existed. Determining the actual aetiology of the left ventricular systolic dysfunction identified in this study is not possible due its design as a cross-sectional survey. Sorting out the relative importance of hypertension and IHD in the aetiology of left ventricular systolic dysfunction, in general, is complex as hypertension is a risk factor for coronary artery disease. In addition, blood pressure may fall once systolic dysfunction and CHF ensue, and so a measured blood pressure at a screening visit may mask a subject's hypertensive past. Also of relevance is the fact that medication for CHF and left ventricular systolic dysfunction also lowers blood pressure. However, despite these limitations, this work does shed light on the relative contributions of these two important risk factors for left ventricular systolic dysfunction in an urban population in the 1990s.

The aetiological factor conferring the greatest odds ratio for left ventricular systolic dysfunction in this study was IHD which was found in 83% of subjects with left ventricular systolic dysfunction. This contrasts with earlier epidemiological work in CHF which implicated IHD as the sole precursor of CHF in only 10% of CHF subjects and IHD accompanied by hypertension in 39% of chronic heart failure (McKee et al. 1971). In this study the combination of hypertension and IHD was a powerful predictor of left ventricular systolic dysfunction, being encountered in 50% of those with left ventricular systolic dysfunction (62% in symptomatic left ventricular systolic

dysfunction and 38% of asymptomatic left ventricular systolic dysfunction). However, hypertension alone, was not more prevalent in subjects with (10%) or without (13%) left ventricular systolic dysfunction. In contrast, hypertension accounted for 75% of the CHF detected in the Framingham study (McKee et al. 1971); it was also the most important independent predictor for the development of CHF in the Gothenburg Study (Eriksson et al. 1989). The results presented here confirm those of others (Ho et al. 1993b,Teerlink et al. 1991) and are likely to reflect a temporal change in the aetiology of CHF, possibly because hypertension has become more readily detected and better treated.

Some recent data from the Framingham Study dispute the more generally held view of IHD being the major cause of CHF (Levy et al. 1996) and still implicate hypertension as the predominant CHF risk factor. However in that publication the definition of hypertension has changed from a blood pressure >160/90 in earlier work to >140/90 in the most recent analysis. As population attributable risk is dependent on the prevalence of the risk factor it is hardly surprising that hypertension is playing such a prominent part when the blood pressure cut-off is reduced to >140/90. In a similar manner to the Framingham paper, this work also shows a dose effect of the degree of hypertension and left ventricular systolic dysfunction. Although the odds ratio for a blood pressure in the range of 140-159 mmHg systolic and/or 90-94 mmHg diastolic was increased, this was not significant until the blood pressure was ≥160 mmHg systolic and/or 95 mmHg diastolic. This is not to say that hypertension should not be regarded as present once a blood

pressure of >140/90 mmHg is reached, but rather in the context of epidemiological studies where blood pressure is being measured at only one visit, the cut-off. of >140/90 mmHg may overestimate the prevalence of hypertension.

The overriding contribution of IHD to left ventricular systolic dysfunction in this study is suggested by the increase in the prevalence of left ventricular systolic dysfunction in the fifth decade for men and the seventh for women. This mirrors the age related increase in prevalence of IHD in this population (Tunstall-Pedoe et al. 1994).

The finding that hypertension and all manifestations of ischaemia become more prevalent in those with symptomatic left ventricular systolic dysfunction compared to asymptomatic left ventricular systolic dysfunction lends support to the theory that further cardiovascular events might be contributing to the progression of left ventricular systolic dysfunction to CHF.

As the predominant determinants of left ventricular systolic dysfunction were IHD and concomitant IHD and hypertension, the need for aggressive primary and secondary prevention of IHD is underscored. Rigorous management of hypertension is important - there is good evidence that treatment of hypertension, with angiotensin converting enzyme inhibitors, in those with left ventricular systolic dysfunction, reduces mortality and morbidity (Kostis, 1995).

Returning to an earlier point made in Chapter 2, the magnitude of the prevalence of both symptomatic and asymptomatic left ventricular systolic

dysfunction demonstrated in this study seriously raises the issue of case-finding for symptomatic and screening for asymptomatic left ventricular systolic dysfunction. The work in this chapter confirms that the majority of those with asymptomatic left ventricular systolic dysfunction have evidence of IHD or hypertension, and therefore, the likelihood is that they would benefit in terms of mortality and morbidity from angiotensin converting enzyme inhibition. The data shown here also suggest that widespread population screening by echocardiography may be unnecessary since 93% of those with left ventricular systolic dysfunction are recognisable clinically. Identification of high risk target groups (those with angina, myocardial infarction, hypertension and diabetes) for further evaluation echocardiographically would be the strategy of choice. Thus, resources should be targeted at these groups to maximise the accurate detection of left ventricular systolic dysfunction leading to better treatment, improved mortality, lower morbidity and reduced health related costs.

Chapter 5

The Effect of Left Ventricular Systolic Dysfunction on Effort Capacity in an Urban Population

5.1 INTRODUCTION

As the cardinal symptoms of CHF occur, at least initially, on exertion, exercise testing would be expected to be useful in its evaluation. Indeed, the response to maximal stress testing provides a means of grading disability and estimating cardiopulmonary reserve in CHF (Zelis et al. 1990). Peak oxygen consumption and exercise duration are reduced, not only in subjects with symptomatic, but also in those with asymptomatic left ventricular systolic dysfunction (LeJemtel et al. 1994). Many studies have shown, in patient groups with symptomatic left ventricular systolic dysfunction, that resting echocardiographic measures of left ventricular function correlate poorly with peak oxygen consumption and exercise duration (Franciosa et al. 1981), nevertheless, both are powerful independent predictors of prognosis in symptomatic left ventricular systolic dysfunction (Cohn et al. 1993) and can be used to estimate the severity of CHF. To date there are no population studies on left ventricular systolic dysfunction, which have also incorporated maximal exercise testing. This chapter reports the first epidemiological work to study the effect of left ventricular systolic dysfunction on effort capacity in a random sample from the general population of both men and women aged 25-74.

5.2 METHODS

5.2.1 Population

This is as described in Chapter 2 and relates to the subjects who had a LVEF (Biplane Simpson's Rule), questionnaire data, a 12 lead ECG and who completed a maximal exercise test.

The definitions of left ventricular systolic dysfunction, symptomatic, asymptomatic, ischaemic heart disease, hypertension and ECG abnormalities are identical to those used in Chapter 3.

The LVEF has been split further into four categories for part of the analysis. These are 1; LVEF>40%, 2; LVEF 36-40%, 3; LVEF 31-35%, 4; LVEF≤30%.

Significant ischaemia on exercise testing has been defined as depression of the ST segment of ≥1mm at any point during the test or in the recovery phase. That ST depression had to be of a horizontal or downward sloping nature.

5.2.2 Statistics

Exercise times are presented as means±SDs. Differences between the means of those with and without left ventricular systolic dysfunction were compared using the Student's t test. The results for the categories (asymptomatic left ventricular systolic dysfunction, symptomatic left ventricular systolic dysfunction and no left ventricular systolic dysfunction) and LVEF categories 1-4 were tested using analysis of variance (ANOVA). A multivariate regression model was used to determine the independent predictors of effort capacity (treated as the dependent variable). P values <0.05 are considered to be significant.

5.3 RESULTS

5.3.1 Characteristics of the Population

1281 (78% of the screened population) subjects completed a maximal exercise test. Their baseline characteristics are shown in Table 5.1.

Table 5.1: Characteristics of the Population (Aged 25-74) Which Underwent Exercise Testing

Age	mean 49.3 (SD14)
Sex	male 47.8% (613)
Evidence of IHD	19.7% (252)
Evidence of MI	5.6% (69)
History of angina	8% (103)
ECG ischaemia	14.4% (181)
ECG abnormal	18.4% (236)
Breathless	7.9% (98)
Hypertension	21% (266)
Diabetes	1.6%(20)
Left ventricular systolic dysfunction (LVSD)	2.2%(28)
Asymptomatic LVSD	57.5% (15)*
Symptomatic LVSD	42.3% (11)*

Legend to Table 5.1: IHD (Ischaemic Heart Disease) refers to either a history of angina or treatment with nitrates or a history of myocardial infarction (MI) or ECG evidence of q waves, left bundle branch block (LBBB) or a significant ST/T segment abnormality. Evidence of MI is defined as a history of MI or the presence of pathological Q waves on the ECG. ECG ischaemia is the presence of a pathological Q wave, LBBB or a significant ST/T segment abnormality. An abnormal ECG is defined as those abnormalities constituting ECG ischaemia and/or the presence of voltage criteria for left ventricular hypertrophy and/or atrial fibrillation/flutter. Breathlessness refers to cardiac dyspnoea according to the MRC Breathlessness Questions (in the absence of cough and/or sputum production for more than 3 days of the week for 3 months of the year). Hypertension is a measured blood pressure of >160mmHg systolic and/or 95mmHg diastolic and or current treatment with an antihypertensive. Diabetes is defined as a history of physician diagnosed diabetes and/or treatment with an oral hypoglycaemic agent and/or insulin. LVSD is a LVEF≤30%. Treated LVSD refers to the prescription of a loop diuretic drug. The figures quoted are percentages with the numbers in parentheses, except for age which is followed by the standard deviation in brackets.*Two subjects had not completed the MRC Breathlessness Questionnaire and could not be assigned as symptomatic/asymptomatic.

5.3.2 Effort Capacity in the Population

The frequency distribution histograms for exercise duration in men and women are depicted in Figures 5.1 and 5.2, respectively. Effort capacity is approximately normally distributed with a tail to the left. The mean exercise durations were 736 secs±163 (SD) for men and 648±154 for women.

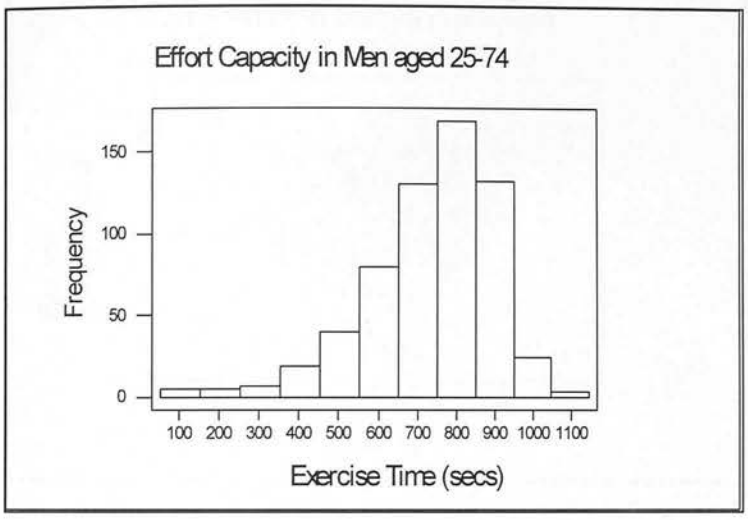
5.3.3 Effort Capacity and Left Ventricular Ejection Fraction

Figures 5.3 and 5.4 show plots of exercise duration and LVEF in men and women respectively. It can be seen that any relationship between LVEF and exercise capacity is most marked in those whose ejection fractions are ≤30%. This is seen more strikingly in Figures 5.5 and 5.6 where LVEF is divided into the categories shown. For both men and women the mean exercise duration is only significantly reduced once the left ventricular ejection fraction is ≤30%.

5.3.4 Effort Capacity and Left Ventricular Systolic Dysfunction

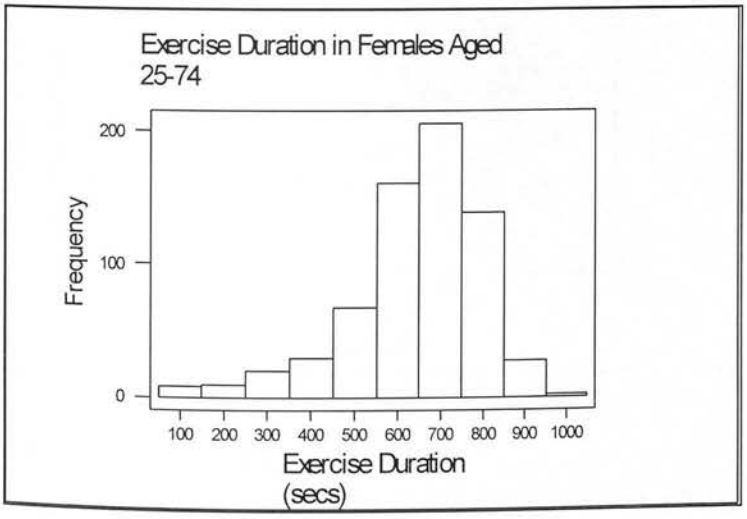
Table 5.2 gives the exercise times for men and women with and without left ventricular systolic dysfunction. In the univariate analysis, a LVEF ≤30% was associated with a significant reduction in the average exercise duration of 134 secs for men ($p=0.0001$) and 294 secs for women ($p=0.001$). Although the mean effort capacity for men and women was less in subjects with asymptomatic left ventricular systolic dysfunction, it was not statistically significant compared to those without systolic dysfunction (regardless of symptoms). When those with asymptomatic left ventricular systolic dysfunction were compared with asymptomatic subjects with a LVEF >30%, the result was significant for men at $p=0.02$ but still failed to achieve statistical significance in women ($p=0.15$).

Figure 5.1.



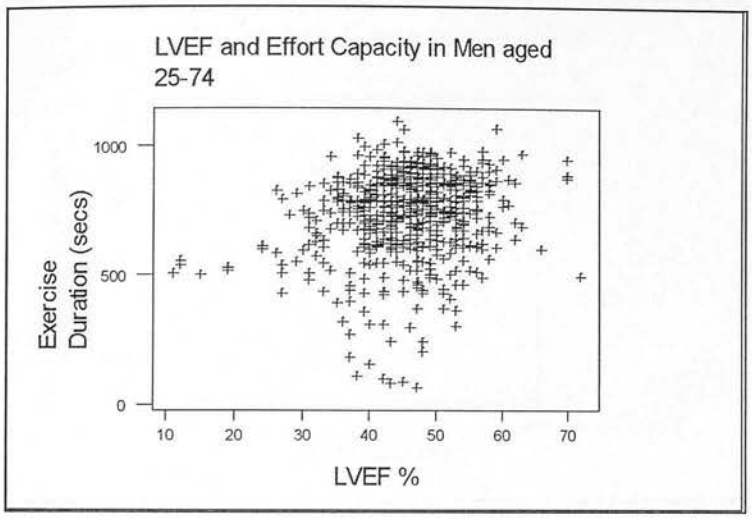
Legend to Fig. 5.1
Frequency distribution histogram for the 613 men undergoing exercise testing. The mean exercise time (secs) was 736, median, 766, standard deviation 163 and range 71 to 1094.

Figure 5.2.



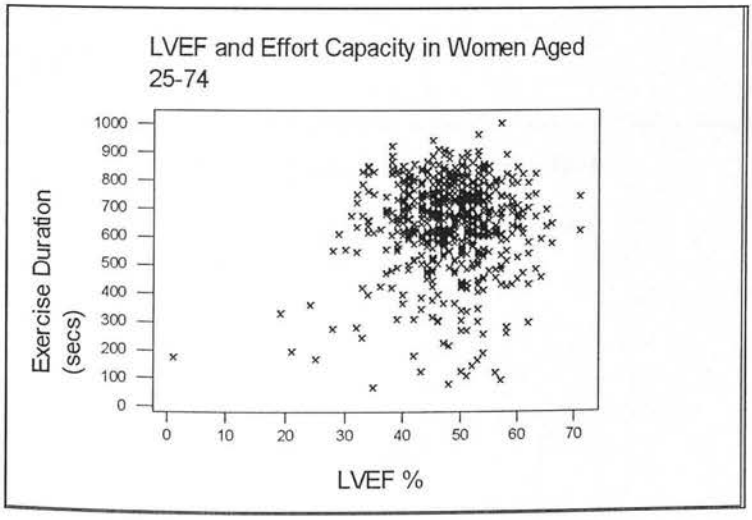
Legend to Fig. 5.2
Frequency distribution histogram for the 668 women undergoing exercise testing. The mean exercise time (secs) was 648, median, 670, standard deviation 154 and range 67 to 1000.

Figure 5.3



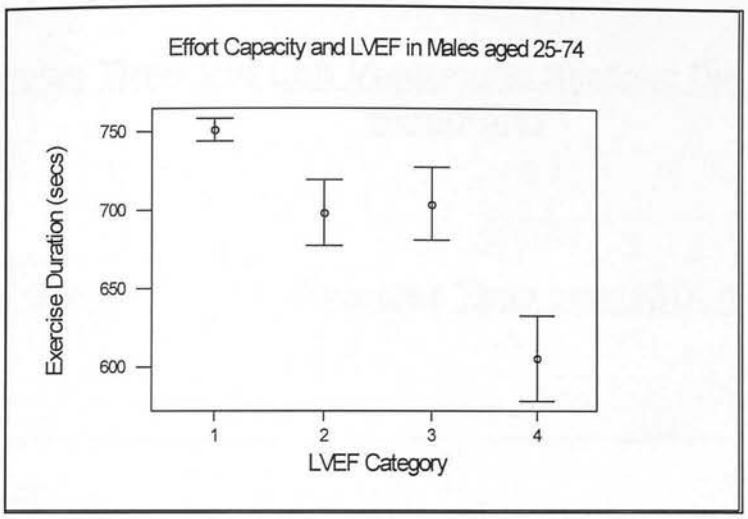
Legend to Fig. 5.3
Exercise duration is expressed in seconds and plotted against LVEF (%) for men.

Figure 5.4



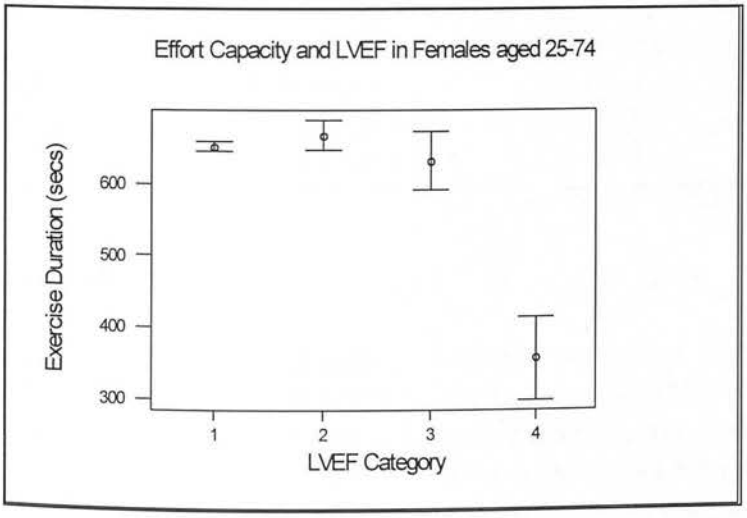
Legend to Fig. 5.4
Exercise duration is expressed in seconds and plotted against LVEF (%) for women.

Figure 5.5



Legend to Fig. 5.5
Mean exercise duration is expressed in seconds ±SEM.
LVEF Category 1=a LVEF>40%, 2=a LVEF of 36-40%, 3=a LVEF 31-35%, and 4=a LVEF≤30%. ANOVA was significant at $p<0.0001$. Only the difference between category 4 and the other 3 categories was statistically significant.

Figure 5.6



Legend to Fig. 5.6
Mean exercise duration is expressed in seconds ±SEM.
LVEF Category 1=a LVEF>40%, 2=a LVEF of 36-40%, 3=a LVEF 31-35%, and 4=a LVEF≤30%. ANOVA was significant at $p<0.0001$. Only the difference between category 4 and the other 3 categories was statistically significant.

Table 5.2

Exercise Time and Left Ventricular Systolic Dysfunction and Symptoms

LVEF Group	Exercise Time secs (SD) n	p value
Males		
LVSD	606 (119) 19	
No LVSD	740 (162) 594	0.0001*
*SLVSD	523 (60) 6	
*ASLVSD	652 (122) 12	
S No LVSD	623 (160) 38	
A No LVSD	747(160) 543	<0.001Ψ
Females		
LVSD	356 (175) 9	
No LVSD	652 (150) 659	0.001*
*SLVSD	299(157) 5	
*ASLVSD	387(211) 3	
S No LVSD	555(187) 67	
A No LVSD	665(140) 571	<0.001Ψ

Legend to Table 5.2

LVSD represents left ventricular systolic dysfunction and refers to a LVEF≤30% irrespective of symptoms. No LVSD is a LVEF>30%, irrespective of symptoms. The letter S denotes "symptomatic" i.e the presence of cardiac dyspnoea or loop diuretic therapy, the letter A signifies asymptomatic subjects i.e those without cardiac dyspnoea and not taking loop diuretics. The *p value refers to a Student's t test between the two means. ψP value denotes ANOVA for the groups shown. Further testing between the individual means SLVSD, ASLVSD and ASLVSD and No LVSD for both men and women was not statistically significant. *Two subjects had not completed the MRC Breathlessness Questionnaire and could not be assigned as symptomatic/asymptomatic.

Table 5.3 shows the mean exercise durations for men and women, divided by age group and the presence or absence of a LVEF≤30% and>30%. Effort capacity diminishes with age and, with the exception of one group in men aged 35-44 (where there is only one subject with left ventricular systolic dysfunction), the presence of left ventricular systolic dysfunction confers a lower mean exercise time.

In a multivariate regression analysis performed on all subjects, the independent predictors of a lower exercise time were increasing age ($p<0.0001$), female sex ($p<0.0001$), current smoking ($p<0.0001$), increasing body mass index ($p<0.0001$), the presence of IHD ($p<0.0001$), left ventricular systolic dysfunction ($p=0.002$) and hypertension ($p=0.038$).

5.3.5 Left Ventricular Systolic Dysfunction and Exercise Induced Ischaemia

The prevalence of ST segment depression in subjects with left ventricular systolic dysfunction was 33% (7/21) compared to 24% (295/1243) in those without left ventricular systolic dysfunction ($P=0.31$ odds ratio [95% confidence intervals] 1.6 [0.6,4.0], Chi square). Men and women either symptomatic or asymptomatic were considered together to provide sufficient numbers for analysis.

Table 5.3

Exercise Time and Left Ventricular Systolic Dysfunction

MALES	Mean Exercise Time in secs.(SD) n	Mean Exercise Time in secs.(SD) n
Age Group	LVEF>30%	LVEF≤30%
25-34	870 (82) 117	
35-44	809 (126) 123	828 1
45-54	739 (136) 113	674 (129) 7
55-64	678 (142) 126	536 (40) 5
65-74	603 (166) 115	547 (61.8) 6

FEMALES	Mean Exercise Time in secs.(SD) n	Mean Exercise Time in secs.(SD) n
Age Group	LVEF>30%	LVEF≤30%
25-34	751 (90) 122	
35-44	766 (104) 154	
45-54	668 (127) 134	420 (196) 4
55-64	591 (149) 128	168 1
65-74	530 (163) 121	339 (158) 4

5.4 DISCUSSION

The results presented in this chapter show, for the first time, that left ventricular systolic dysfunction, in subjects randomly sampled from the general population significantly impairs effort capacity. The average reduction for men was over 2 minutes, and for women nearly 5 minutes, less than subjects whose left ventricular ejection fraction was >than 30%.

The data for symptomatic left ventricular systolic dysfunction show a marked reduction compared to those without left ventricular systolic dysfunction in keeping with the syndrome of CHF severely limiting physical functioning (Stewart et al. 1989). Also of importance is the finding that asymptomatic individuals with left ventricular systolic dysfunction had a trend towards reduced effort capacity (a reduction of 88 secs in men and 265 secs in women). This was more impressive if compared with the effort capacities of asymptomatic subjects within the general population (a reduction of 95 secs for men and 275 secs for women) when the findings did achieve statistical significance for men. The lack of statistical significance in women is almost certainly due to the small numbers with asymptomatic left ventricular systolic dysfunction. This observation lends weight to the earlier hypothesis, in this thesis, that the asymptomatic left ventricular systolic dysfunction identified in this study is biologically important. As both reduced ejection fraction and decreased exercise duration are powerful independent predictors of prognosis in symptomatic left ventricular systolic dysfunction, the finding of both these variables being depressed in asymptomatic left ventricular systolic

dysfunction in this population suggests that the likely natural history of the asymptomatic left ventricular systolic dysfunction will be progression to CHF.

In CHF where evaluation of symptoms is too subjective to judge severity, exercise testing remains an important means of assessing functional capacity. In this study, we have confirmed using an objective method that the left ventricular systolic dysfunction identified is associated with a significant impairment of aerobic capacity. The STEEP Protocol, used in this work, generates a linear relationship between oxygen consumption and exercise duration, allowing the latter to be used as a surrogate for peak VO_2 (Northridge et al. 1990, Riley et al. 1992). Translating the exercise durations in those with left ventricular systolic dysfunction to oxygen uptakes reveals the extent of impairment in aerobic capacity which was found. Thus for symptomatic left ventricular systolic dysfunction the mean peak VO_2 was 18mls/kg/min for men and 12mls/kg/min for women and for asymptomatic left ventricular systolic dysfunction, it was 22mls/kg/min in men and 15mls/kg/min in women.

Comparisons with other work are limited due to the unique combination of exercise testing and echocardiography in this cross-sectional population sample. This study has reproduced the poor correlation between resting left ventricular ejection fraction and exercise capacity, when treated as a continuous variable (Franciosa et al. 1981) but shown the expected relationship between a reduced left ventricular ejection fraction and effort capacity.

The decision to choose an ejection fraction cut-off of ≤30% is vindicated by the exercise results. Effort capacity was not significantly reduced until a value of ≤30% was reached.

The earlier finding of IHD being the predominant determinant of left ventricular systolic dysfunction in this population was also confirmed by the finding that half the subjects with left ventricular systolic dysfunction had evidence of exercise induced significant ST segment depression.

This chapter, by demonstrating that effort capacity is reduced in those with ejection fractions ≤30%, adds to the total picture of left ventricular systolic dysfunction in this population by highlighting that the physical debility caused by symptomatic left ventricular systolic dysfunction is also present, albeit to a lesser degree, in asymptomatic left ventricular systolic dysfunction. That the left ventricular systolic dysfunction identified was significantly associated with ischaemia confirms that the left ventricular systolic dysfunction in this community would be worthy of further investigation and management.

Chapter 6

Biochemical Detection of Left Ventricular Systolic Dysfunction in an Urban Population

6.1 INTRODUCTION

The syndrome of chronic heart failure (CHF) is a common, lethal and disabling condition, mainly attributable to left ventricular systolic dysfunction (McKee et al. 1971, The SOLVD Investigators, 1991). CHF, itself, often lies at the end stage of a progressive deterioration of LV function, which can remain asymptomatic for years. The work presented earlier in this thesis has shown that the asymptomatic form of left ventricular systolic dysfunction is as prevalent as CHF. We now, also, have compelling evidence demonstrating that treatment with ACE inhibitors reduces mortality and morbidity in patients with left ventricular systolic dysfunction, be it symptomatic or asymptomatic (Swedberg et al. 1987, The SOLVD Investigators, 1992).

Detecting those with symptomatic and asymptomatic left ventricular systolic dysfunction is crucial in reducing the substantial mortality and morbidity associated with CHF. However, the clinical diagnosis of CHF is unreliable (Wheeldon et al. 1993a) and the asymptomatic precursor is clinically silent. While population screening by echocardiography might provide a solution, it would not be a cost effective one - a biochemical option would seem more attractive.

The C and N terminals of atrial natriuretic peptide (C-ANP and N-ANP) are predominantly secreted by the atria in response to the stretch which occurs with the increased left atrial pressure associated with CHF (Glenbotski et al. 1988). The circulating concentrations of both these peptides are raised in patients with symptomatic left ventricular systolic dysfunction (Francis et al. 1990, Lerman et al. 1993). The levels of N-ANP are higher reflecting its

longer half life due to reduced renal clearance (Sundsfjord et al. 1988). More recently plasma concentrations of brain natriuretic peptide (BNP), predominantly produced by the ventricles, have also been shown to be elevated in patients with symptomatic left ventricular systolic dysfunction (Wei et al. 1993, Motwani et al. 1993). Moreover, N-ANP and BNP concentrations are also raised in patients with asymptomatic left ventricular systolic dysfunction (Lerman et al. 1993, Motwani et al. 1993).

No previous work has addressed the question of population screening for left ventricular systolic dysfunction using the natriuretic peptides. This chapter reports on the first epidemiological study in which the utility of N-ANP and BNP to identify left ventricular systolic dysfunction has been evaluated.

6.2 METHODS

The methods involved are as described in the Chapter 2: it involves 1252 subjects who had an analysable echocardiogram (LVEF, a questionnaire, ECG and a venous blood sample available for measurement of plasma N-terminal atrial natriuretic peptide (N-ANP) and brain natriuretic peptide (BNP).

6.2.1 Definitions

IHD is defined as a history of angina and/or current use of nitrates and/or a history or ECG evidence of MI and/or ECG criteria for major or minor ischaemia. Left ventricular systolic dysfunction pertains to a LVEF≤30%.

6.2.2 Statistics

Natriuretic peptide concentrations are expressed as medians with interquartile ranges in parentheses. Differences in concentration between the

natriuretic peptides in those with and without significant left ventricular systolic dysfunction and between those with symptomatic and asymptomatic left ventricular systolic dysfunction compared to those with normal LV function were tested using the Kruskall-Wallis test. Differences between the individual categories of LVEF (1-4) were assessed overall by the Kruskall-Wallis test, differences between the individual categories e.g. 1 and 2, 2 and 3, and 3 and 4 were compared using the Mann-Whitney U test. A multiple logistic regression model was used to determine independent predictors of left ventricular systolic dysfunction. Variables included in the model were a history of MI, a history of angina, hypertension, an "abnormal ECG", BNP and N-ANP concentrations. Receiver operator characteristic (ROC) curves were constructed to determine the sensitivity and specificity of BNP and N-ANP throughout the range of concentrations to detect left ventricular systolic dysfunction. The area under the ROC curve (AUC) was estimated according to the method of Hanley and McNeill (Hanley and McNeill, 1982) and provides a measure of the overall diagnostic accuracy of the test. The optimum BNP concentration for the calculation of positive and negative predictive accuracies was determined from the ROC analysis by addition.

6.3 RESULTS

Table 6.1 shows the characteristics of the study population. 1252 subjects had an analysable echocardiogram, a questionnaire, ECG and a venous blood sample available.

Table 6.1: Characteristics of the Population (Aged 25-74)

Age	mean 50.9 (SD14)
Sex	male 49.1% (615)
Evidence of IHD	24% (289)
Evidence of MI	4.3% (80)
History of angina	11% (134)
ECG ischaemia	14.6% (179)
ECG abnormal	21.9% (268
Breathless	10%(122)
Hypertension	23.5% (291)
Diabetes	2.6%(32)
Left ventricular systolic dysfunction (LVSD)	3.0%(37)
Asymptomatic LVSD	51% (19)
Symptomatic LVSD	49% (18)
Cardiac Dyspnoea	5
Treated	8
Treated and Dyspnoeic	4

Legend to Table 6.1: IHD (Ischaemic Heart Disease) refers to either a history of angina or treatment with nitrates or a history of myocardial infarction (MI) or ECG evidence of q waves, left bundle branch block (LBBB) or a significant ST/T segment abnormality. Evidence of MI is defined as a history of MI or the presence of pathological Q waves on the ECG. ECG ischaemia is the presence of a pathological Q wave, LBBB or a significant ST/T segment abnormality. An abnormal ECG is defined as those abnormalities constituting ECG ischaemia and/or the presence of voltage criteria for left ventricular hypertrophy and/or atrial fibrillation/flutter. Breathlessness refers to cardiac dyspnoea according to the MRC Breathlessness Questions (in the absence of cough and/or sputum production for more than 3 days of the week for 3 months of the year). Hypertension is a measured blood pressure of >160mmHg systolic and/or 95mmHg diastolic and or current treatment with an antihypertensive. Diabetes is defined as a history of physician diagnosed diabetes and/or treatment with an oral hypoglycaemic agent and/or insulin. LVSD is a LVEF≤30%. Treated LVSD refers to the prescription of a loop diuretic drug. The figures quoted are percentages with the numbers in parentheses, except for age which is followed by the standard deviation in brackets.

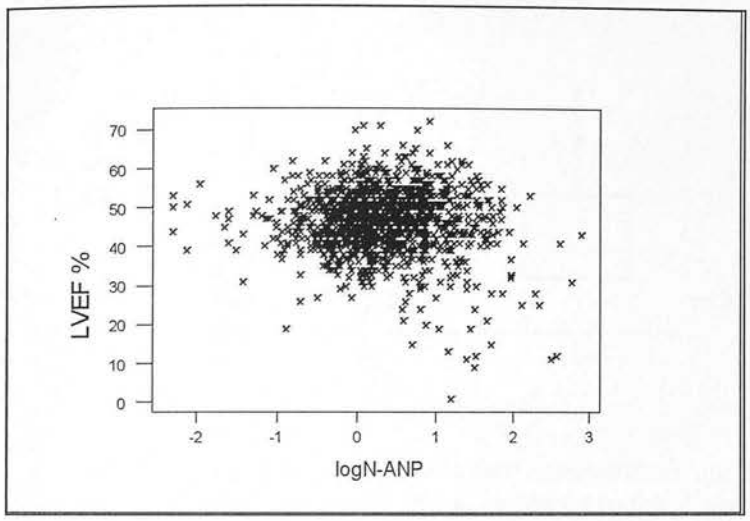
Thirty five subjects (3.0%) had significant left ventricular systolic dysfunction of whom 51% (19) were symptomatic, 49% (18) were asymptomatic.

Neither N-ANP or BNP were normally distributed. Log (e) transformation resulted in a normal distribution. Figures 6.1 and 6.2 show the scatter plots for log N-ANP and log BNP plotted against LVEF. It can be seen that any relationship that does exist between these variables is concentrated where the ejection fraction is lowest.

The median concentration (interquartile range) of N-ANP in those with left ventricular systolic dysfunction was 2.8 (1.8,4.6) ng/ml compared to 1.3 (0.9,1.8) ng/ml in those without left ventricular systolic dysfunction ($p<0.001$) (Figure 6.3). In subjects with symptomatic left ventricular systolic dysfunction, it was 3.3 (2.4,5.4) and in those with asymptomatic left ventricular systolic dysfunction, 2.2 (1.2,4.5) ng/ml. The BNP concentration, was similarly, significantly higher in subjects with left ventricular systolic dysfunction: 24.0 (18,33) pg/ml compared to those with normal LV function: 7.7 (3.4,13) pg/ml, $p<0.001$.(Figure 6.4). The BNP concentration was highest in those with symptomatic left ventricular systolic dysfunction; 25(20, 33) and was lower in those with asymptomatic left ventricular systolic dysfunction; 23.4 (13.7,35.2), $p<0.001$.

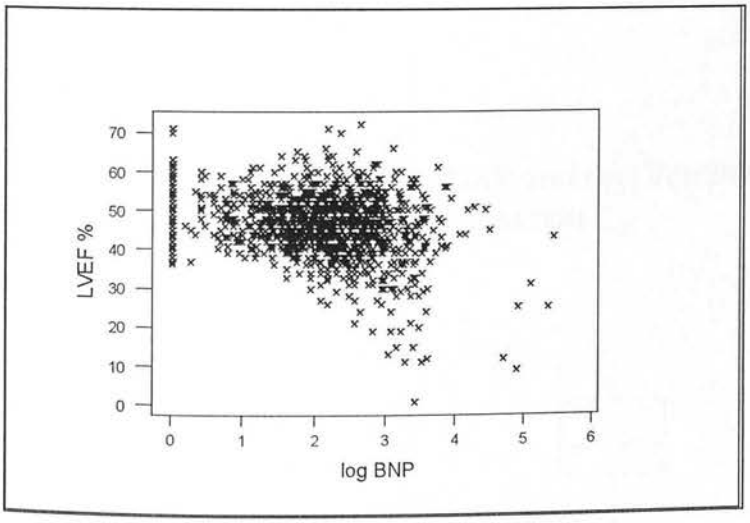
Figure 6.5 shows that the median concentration of N-ANP is only significantly raised once the LVEF is $\leq 30\%$ ($p=0.0002$) when compared with the category LVEF of 31-35%. The difference between those with an ejection fraction in the range 31-35% and 36-40% was not significant ($p=0.5$). The same analysis for BNP is depicted in Figure 6.6. However, the BNP median

Figure 6.1 N-ANP and Left Ventricular Ejection Fraction



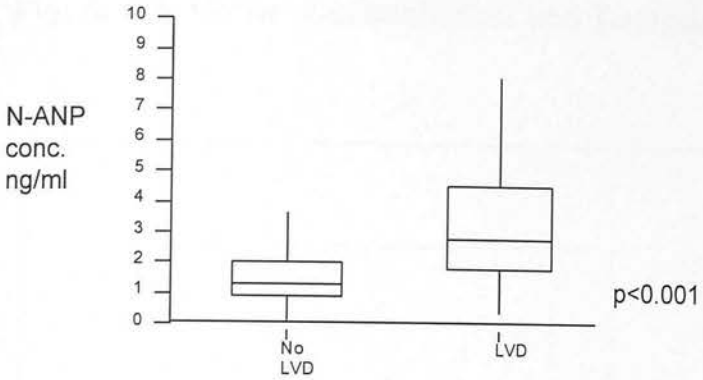
Legend to Figure 6.1 Log N-ANP conc. (ng/ml) plotted against LVEF (%) for all subjects aged 25-74.

Figure 6.2 BNP and Left Ventricular Ejection Fraction



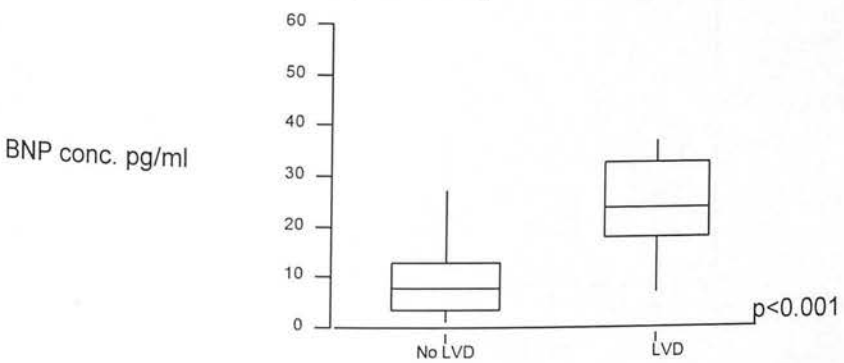
Legend to Fig 6.2 Log BNP conc.(pg/ml) plotted against LVEF (%) for all subjects aged 25-74.

Figure 6.3: N-ANP and Left Ventricular Systolic Dysfunction



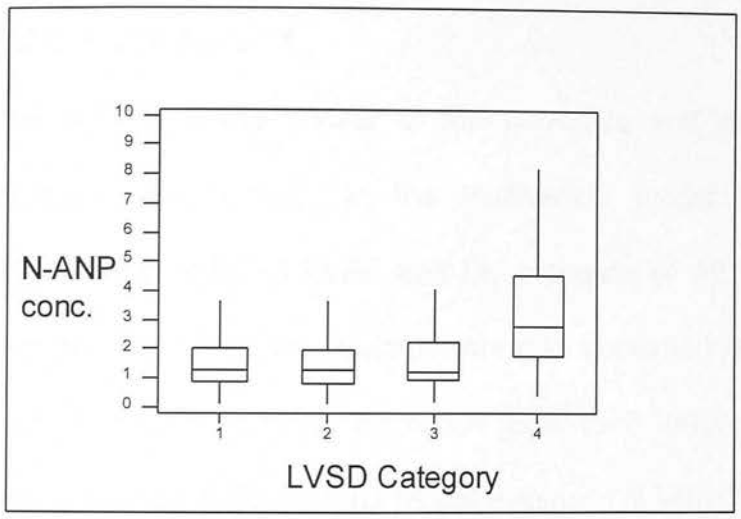
Legend to Fig 6.3: N-ANP concentrations are expressed as medians with the interquartile ranges displayed by the box and the range of concentrations by the vertical lines.

Figure 6.4: BNP and Left Ventricular Systolic Dysfunction



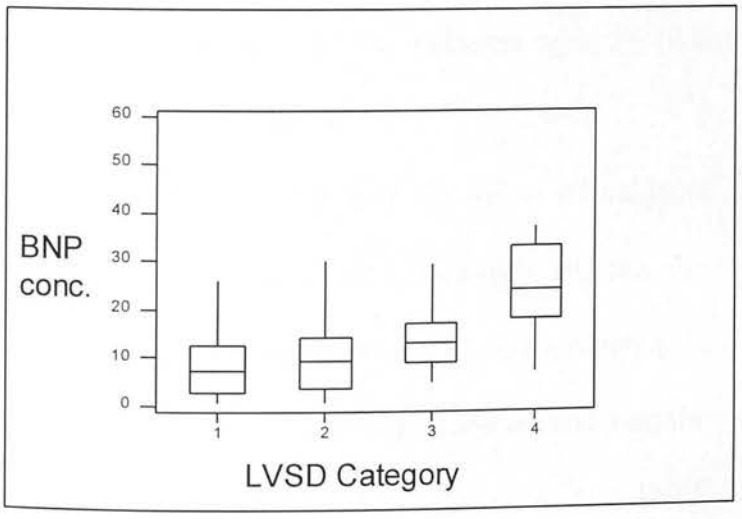
Legend to Fig 6 4:BNP concentrations are expressed as medians with the interquartile ranges displayed by the box and the range of concentrations by the vertical lines.

Figure 6.5 N-ANP Concentration and Categories of LVEF



Legend to Figure 6.5: N-ANP concentrations are expressed in ng/ml as medians ± interquartile ranges (box). The range is displayed by the vertical line. Left ventricular systolic dysfunction (LVSD) Category 1 is>40%, 2=36-40%,3=31-35% and 4=≤30%.

Figure 6.6 BNP Concentration and Categories of LVEF



Legend to Figure 6.6: BNP concentrations are expressed in pg/ml as medians ± interquartile ranges (box). The range is displayed by the vertical line. Left ventricular systolic dysfunction (LVSD) Category 1 is>40%, 2=36-40%, 3=31-35% and 4=≤30%.

concentration for the LVEF category 31-35% [13(9,17)] is significantly higher than that obtained with a LVEF of 36-40% [9.2(3.7,14.3)] p=0.0001. It is only marginally elevated in the category 36-40% compared to those with a LVEF>40% [7.2(3.1,12.4)] p=0.04.

Tables 6.2 and 6.3 show the results of the univariate and multivariate regression analyses, respectively. In the multivariate model the most significant predictor of a reduced LVEF was the presence of IHD. A 50% increase in BNP and N-ANP concentrations were also powerful independent predictors of left ventricular systolic dysfunction [BNP (p=0.0001) or N-ANP (p=0.0001)]. The presence of BNP in the model displaced N-ANP. The odds ratio for a BNP increase of 50% being associated with left ventricular systolic dysfunction was 1.9 [1.5,2.4].

Figures 6.7, 6.8, 6.9 and 6.10 show ROC curves for varying concentrations N-ANP and BNP in diagnosing left ventricular systolic dysfunction in the entire population aged 25-74, those over 55 yrs, subjects aged 25-74 with IHD and subjects >55yrs with IHD, respectively.

The area under the curves for BNP and N-ANP in all subjects, those ≥55 years, those with IHD, and subjects ≥55 years with IHD are shown in Table 6.4. BNP is superior to N-ANP in detecting systolic dysfunction.

Table 6.5 gives the sensitivity, specificity, positive and negative predictive accuracies for a BNP of ≥17.9pg/ml in the detection of a LVEF≤30%. For diagnosing left ventricular systolic dysfunction in all subjects aged 25-74, the sensitivity was 76% (specificity 87%). Confining the analysis to subjects aged 25-74 with IHD gave a superior sensitivity of 84% (specificity 76%) in

Table 6.2 : Univariate Logistic Regression Analysis

Variable	p value	Odds Ratio [95% Confidence Intervals]
Sex (male)	0.013	2.4 [1.2,4.8]
Age	0.0001	1.07[1.04,1.10]
Diabetes	0.0001	12.5[5.3,33.3]
Breathlessness	0.005	3.0[1.4,6.6]
ECG Abnormality	0.0001	8.3[4.2,16.7]
IHD	0.0001	20.0[7.7,50.0]
Hypertension	0.0001	5.6[2.9,11.1]
BNP	0.0001	2.0[1.7,2.5]
N-ANP	0.0001	1.8[1.5,2.2]

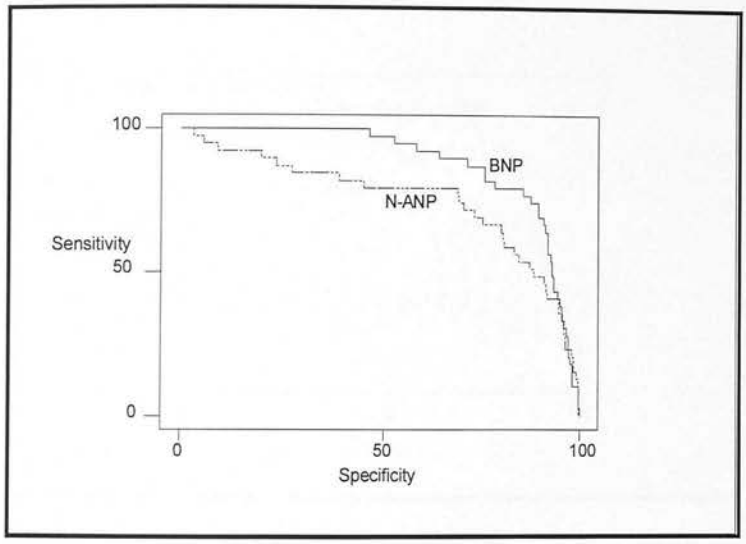
Legend to Table 6.2: IHD is ischaemic heart disease. The definitions of the variables are contained in the legend to Table 1. The p values for BNP and N-ANP are for concentrations of the peptides which are increased by 50%.

Table 6.3: Multivariate Logistic Regression Analysis

Variable	p value	Odds Ratio [95%CI]
Sex(male)	0.008	3.1 [1.4,7.1]
Diabetes	0.004	5.0 [1.7,14.3]
IHD	0.0001	7.7. [2.9, 20.0]
BNP	0.0001	1.9 [1.5,2.4]

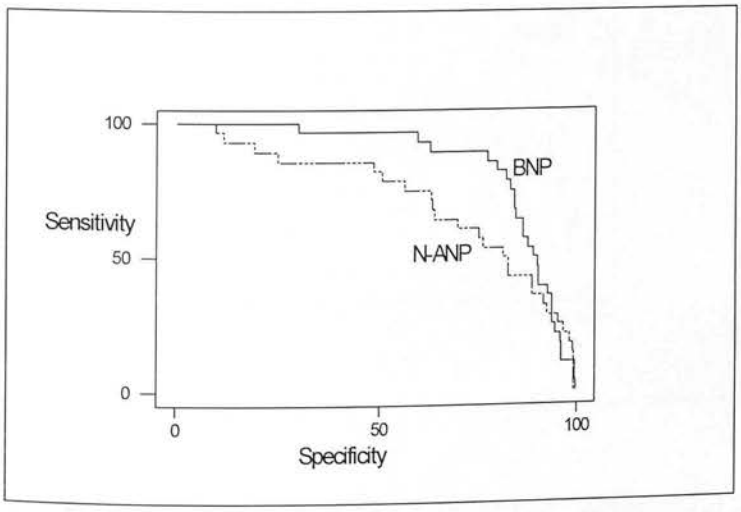
Legend to Table 6.3:
IHD refers to ischaemic heart disease. The definitions are the same as in the legend to Table 1. BNP refers to a 50% increase in the concentration of Brain Natriuretic Peptide. The odds ratios are quoted with the 95% confidence intervals [CI] in parentheses.

Figure 6.7: Receiver Operator Characteristic Curve for BNP and N-ANP in the Detection of Left Ventricular Systolic Dysfunction in all Subjects Aged 25-74.



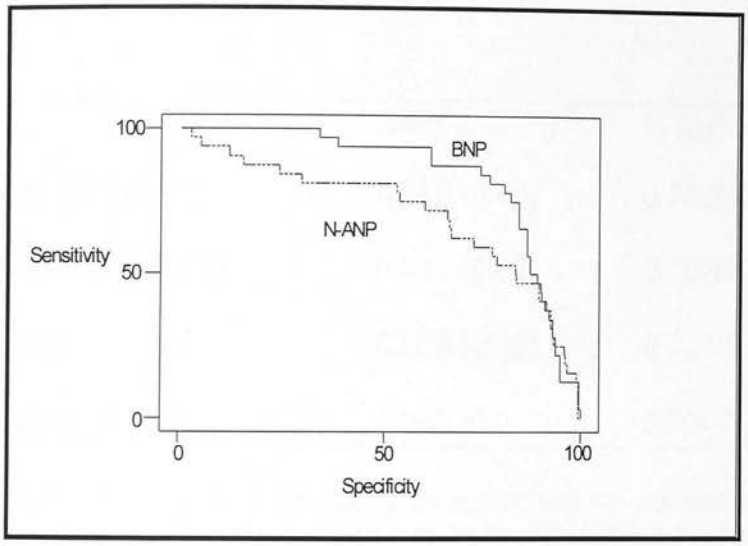
Legend to Figure 6.7: Receiver Operator Characteristic (ROC) Curves for varying concentrations of BNP (solid lines) and N-ANP (broken lines) to detect left ventricular systolic dysfunction in subjects aged 25-74

Figure 6.8: Receiver Operator Characteristic Curve for BNP and N-ANP in the Detection of Left Ventricular Systolic Dysfunction in all Subjects Over 55 Yrs.



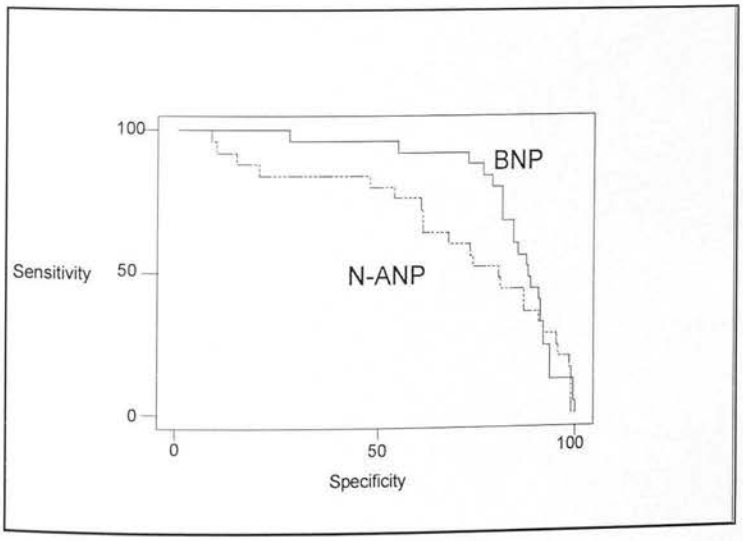
Legend to Figure 6.8: Receiver Operator Characteristic (ROC) Curves for varying concentrations of BNP (solid lines) and N-ANP (broken lines) to detect left ventricular systolic dysfunction in subjects aged over 55 yrs.

Figure 6.9: Receiver Operator Characteristic Curve for BNP and N-ANP in the Detection of Left Ventricular Systolic Dysfunction in Subjects Aged 25-74 With IHD.



Legend to Figure 6.9: Receiver Operator Characteristic (ROC) Curves for varying concentrations of BNP (solid lines) and N-ANP (broken lines) to detect left ventricular systolic dysfunction in subjects aged 25-74 with IHD.

Figure 6.10: Receiver Operator Characteristic Curve for BNP and N-ANP in the Detection of Left Ventricular Systolic Dysfunction in Subjects Over 55 Yrs With IHD.



Legend to Figure 6.10: Receiver Operator Characteristic (ROC) Curves for varying concentrations of BNP (solid lines) and N-ANP (broken lines) to detect left ventricular systolic dysfunction in subjects over 55 yrs with IHD.

Table 6.4: Areas Under Receiver Operator Characteristic Curves

Population	BNP	N-ANP
All subjects aged 25-74	0.882 (0.03)	0.753(0.05)
Subjects aged 25-74 with IHD	0.841 (0.03)	0.709(0.06)
Subjects ≥55 years	0.858 (0.03)	0.723(0.05)
Subjects ≥55 years with IHD	0.843 (0.03)	0.704 (0.06)

Legend to Table 6.4: The areas under the curves are quoted with the standard deviation in parentheses. IHD refers to ischaemic heart disease as described in the methods section.

Table 6.5: Accuracy of BNP in the Detection of Left Ventricular Systolic Dysfunction in Subgroups

Group	Sensitivity	Specificity	Positive Predictive Accuracy	Negative Predictive Accuracy	Prevalence of LVSD
25-74yrs	76%	87%	16%	99.1%	3.2%
>55yrs	89%	71%	18%	99.2%	5.4%
25-74 +IHD	84%	76%	30%	97.5%	11%
>55+IHD	92%	72%	32%	98.5%	12.1%

Legend to Table 6.5: The definition of left ventricular systolic dysfunction (LVSD) is a LVEF≤30%. The BNP concentration cut-off used was a conc .≥17.9pg/ml. IHD refers to any manifestation of ischaemic heart disease as described in the methods section.

detecting left ventricular systolic dysfunction. Restriction of the analysis to subjects ≥55 years is associated with an improvement in the sensitivity to 89% (specificity 71%). Targeting the analysis further to subjects ≥55 years who have IHD results in the optimum sensitivity of 92% with a reduction in specificity to 72%. Defining left ventricular systolic dysfunction as a LVEF≤35%, BNP still performs better than N-ANP. A BNP concentration of ≥17.9pg/ml results in a 43% sensitivity (specificity 88%) in the detection of a LVEF≤35%. This pattern of a lower sensitivity with a specificity, similar to that obtained with a LVEF≤30%, is found in all age groups, irrespective of the IHD status.

Combining the two peptides i.e using a BNP concentration of ≥17.9pg/ml and/or a N-ANP concentration of ≥1.76ng/ml does result in an improved sensitivity for the detection of left ventricular systolic dysfunction in the entire population, the combination is 84% sensitive (66% specific). However, in all age groups, and irrespective of the IHD status, the specificity is less. Analysis based on logistic regression did not reveal any added predictive value of N-ANP after BNP was included in the model.

6.4 DISCUSSION

This work presented in this chapter confirms that BNP and N-ANP concentrations are elevated in subjects with LV systolic dysfunction. Importantly, they are also raised in subjects with asymptomatic left ventricular systolic dysfunction. While this fact has been demonstrated in patient populations, particularly, post myocardial infarction, this work is the first to

report that asymptomatic subjects with left ventricular systolic dysfunction, sampled from the general population have high circulating levels of natriuretic peptides.

The results presented in this chapter also have bearing on the left ventricular ejection fraction cut-off below which left ventricular systolic dysfunction can be said to be present in this population. N-ANP does not become significantly elevated until the ejection fraction is ≤30%, which lends weight to the earlier decision to choose values below this cut-off to indicate definite left ventricular systolic dysfunction. However, it is apparent that BNP is significantly elevated in subjects whose left ventricular ejection fraction is in the range of 31-34% (although the median value is much less). Indeed the average BNP concentration in subjects whose ejection fraction is between 35 and 40% is still marginally, though significantly higher, than those above 40%. This should serve to reiterate the earlier point that the cut point chosen for definite left ventricular systolic dysfunction is both arbitrary and strict. Undoubtedly, there are some subjects in the range of 31-40% who have biologically abnormal ventricular function. The fact that BNP is raised and not N-ANP presumably reflects its ventricular origin. It appears, in this work, to be a more sensitive indicator of ventricular dysfunction. This work also calls into question the currently accepted gold standards for left ventricular systolic function. It is clear that there is no absolute cut-off below which left ventricular systolic dysfunction can be definitely said to be present. It may depend on the premorbid value such that 43% for a person who was at 65%

could be significant. BNP, itself, may prove to be a superior marker of LV function than echocardiographic ejection fraction.

A raised BNP concentration appears to have greater accuracy than N-ANP in detecting left ventricular systolic dysfunction. This is in agreement with the work of others where BNP is emerging as a superior diagnostic marker of left ventricular systolic dysfunction (Wei et al. 1993, Yamamoto et al. 1996, Omland et al. 1996b) although in one post MI study N-ANP was more closely associated with a reduced left ventricular ejection fraction (Omland et al. 1996a).

This study also shows that BNP has acceptable accuracy to be used as a diagnostic tool for detecting left ventricular systolic dysfunction in the whole population. However, widespread population screening for left ventricular systolic dysfunction is unlikely to be cost effective. Targeting the use of this test to individuals at high risk of developing left ventricular systolic dysfunction would lead to a more economical use of further investigation such as echocardiography or radionuclide ventriculography. This work and others have shown that the prevalence of CHF and left ventricular systolic dysfunction rises with age (McKee et al. 1971). The present data confirms that tailoring the analysis to subjects of 55 years and over improves the sensitivity of the test. As 83% of subjects with left ventricular systolic dysfunction had some evidence of IHD (93% of those $\geq$ 55 years), further restriction of the screening to older subjects with IHD results in the optimum sensitivity of the test at 92% with a reduction in the specificity to 72%. It should also be noted from the logistic regression model that BNP does add

incremental value to IHD in the detection of left ventricular systolic dysfunction.

As this is the first study to investigate the use of peptides as screening tools in the general population, comparison with other studies which have addressed this in patient populations poses some problems. Omland et al (Omland et al. 1996b) found the overall accuracy of BNP in detecting mild left ventricular systolic dysfunction (defined as an angiographic LVEF≤45%) in subjects undergoing routine cardiac catheterisation to be only modest (AUC 0.789) in comparison to these results. This may be explained by this study seeking to find significant systolic dysfunction- an ejection fraction ≤30%. This was chosen as a cut off value as it represented a significant (33%) reduction on the mean value for LVEF in this population where it is reasonably certain that true biological and not merely statistical abnormality has been detected (LVEF was normally distributed). Differences in the methods used to determine left ventricular function between studies e.g. echocardiography, radionuclide ventriculography or angiography (which have known discrepancies in the normal range of ejection fraction) diminish the value of comparisons of absolute sensitivity and specificity. Bearing this in mind, these results are similar to those of Yamamoto et al (Yamamoto et al. 1996) who quoted BNP as having a 81% sensitivity (specificity 81%) and N-ANP as 67% sensitive (63% specific) in diagnosing a LVEF≤45% in 94 subjects undergoing cardiac catheterisation for suspected cardiac disease. This work is also comparable to that of Davis et al (Davis et al. 1994) who report a BNP concentration of >22pg/ml as having an 80% sensitivity (70% specificity) for

diagnosing left ventricular systolic dysfunction, defined as a LVEF≤50% in an acutely breathless group of patients. However, in that study BNP had an impressive 93% sensitivity (specificity 90%) for diagnosing heart failure as the cause of dyspnoea.

The results obtained in this study using BNP to detect left ventricular systolic dysfunction in the general population are also similar to work which has examined its use in the post infarct population (Choy et al. 1994)

The results for N-ANP are much less encouraging than those of Lerman et al (Lerman et al. 1993) where N-ANP had both a sensitivity and specificity of >90% for detecting asymptomatic left ventricular systolic dysfunction. This may be due to the low values of N-ANP in the control group in that study. In the present study there is a considerable scatter of both BNP and N-ANP concentrations in those without left ventricular systolic dysfunction. This may reflect the fact that, owing to the study design, sampling had to be carried out at varying times throughout the day. In addition, in this work the values obtained for the natriuretic peptides are not age corrected and the study did not employ any of the usual exclusion criteria applied to those taking part in clinical trials e.g. renal failure. These data, as such, provide an insight into the use of these peptides in routine clinical practice. The sensitivity results for BNP in the general population represent the "worst case scenario" as they will include some individuals with left ventricular systolic dysfunction on treatment for CHF and who may well have low BNP values. Similarly, an elevated BNP concentration in the absence of left ventricular systolic dysfunction could represent a false positive result. Alternatively, the result could be

misclassified due to the strict definition of systolic dysfunction used or could be elevated as a result of left ventricular hypertrophy or renal dysfunction. The very high negative predictive value of BNP in the detection of left ventricular systolic dysfunction gives the best insight into how this test might be used clinically: a BNP concentration of <17.9pg/ml in this study meant the presence of left ventricular systolic dysfunction was highly unlikely.

The meticulous handling of the samples, employed in this work (from supine patients, immediate spinning in a refrigerated centrifuge and plasma storage at -20 °C) would not be acceptable in the primary care setting. However, it is now well known that N-ANP and BNP have impressive in vitro stability (Omland et al. 1996a, Davidson et al. 1995, Murdoch et al. 1997b) allowing meaningful measurements to be performed in blood which has been stored for up to 72 hours. Results in this work were also obtained using radioimmunoassays for N-ANP and BNP which required prior extraction - a time consuming process which would restrict the use of this measurement to specialist tertiary referral centres. Rapid direct assays for these peptides are now available and would widen their possible use making them suitable for use in primary care.

The accuracy of BNP for the detection of left ventricular systolic dysfunction is comparable with that of prostate specific antigen (AUC of 0.94) (Jacobsen et al. 1996) and is superior to mammography for breast carcinoma (0.85) (Swets et al. 1991) and Papanicolaou smears (0.70) (Fahey et al. 1995). The accuracy of prostate specific antigen can be improved by using age specific cut-offs to improve the sensitivity in younger men and the specificity in older

subjects to improve the cost effectiveness of the test. Similar refining of the BNP assay might improve its cost effectiveness.

CHF is a common, serious condition, with a recognisable latent phase which has a treatment known to both reduce mortality and progression. This chapter has shown that detecting symptomatic individuals or screening high risk subjects for left ventricular systolic dysfunction using elevated plasma concentrations of natriuretic peptides merely awaits the further development of a "near patient" assay accessible to primary care physicians.

Chapter 7

The Effect of the Angiotensin Converting Enzyme Insertion/Deletion Polymorphism on Left Ventricular Systolic Dysfunction in an Urban Population

7.1 INTRODUCTION

The renin angiotensin system plays an important role in regulating ventricular structure and function (Harrap et al. 1996, Foult et al. 1988). Angiotensin II has trophic effects on cultured cardiomyocytes (Baker and Aceto, 1990). Experimentally, it causes ventricular hypertrophy by an action which may be largely independent of its pressor effects (Geenen et al. 1990) Similarly, in healthy young adults plasma angiotensin II concentration correlates with left ventricular mass, independently of systolic blood pressure (Harrap et al. 1996). Conversely, a non-hypotensive dose of an ACE inhibitor can regress left ventricular hypertrophy (Slinz et al. 1992). Angiotensin II also has a positive inotropic effect and, in humans, intracoronary administration of an ACE inhibitor reduces cardiac contractility (Foult et al. 1988, Schomish et al. 1990).

Recently, an insertion deletion (I/D) polymorphism related to the presence/absence of a 287 bp fragment in the 16th intron of the angiotensin converting enzyme (ACE) gene has been identified (ACE/I/D polymorphism) (Rigat et al. 1990). The deletion (D) is codominantly associated with circulating ACE concentration and activity, whereby homozygotes for the D allele have a mean serum ACE activity which is almost fifty percent higher than that of subjects with the II genotype (Rigat et al. 1990). ACE activity in tissues, including myocardium, is also increased in D allele homozygotes (Costerousse et al. 1993, Danser et al. 1995).

The rate of conversion of angiotensin I to angiotensin II is increased in the small arteries from subjects with the D allele, as is the physiological response

to angiotensin I (Buikema et al. 1996). These observations suggest that the ACE I/D polymorphism might also influence ventricular structure and function. This part of the study investigates the relationship between the ACE I/D polymorphism, left ventricular mass and left ventricular ejection fraction in a large cross-sectional population study.

7.2. METHODS

7.2.1 Subjects and Population

The study population is described in Chapter 2. The definition of IHD, hypertension and ECG abnormalities are identical to those used earlier.

7.2.2 Statistical Analysis

The analyses were based on the calculation of odds ratios to provide an estimate of relative risk for the various manifestations of "coronary heart disease" i.e MI, ECG major or minor ischaemia. The effect of the ACE D allele was assumed to be co-dominant with codes 0,1 or 2 being applied according to the number of D alleles. The association between the ACE genotypes and left ventricular ejection fraction was determined by linear regression analysis. A p value of <0.05 is taken as statistical significance.

7.3 RESULTS

7.3.1 Baseline Characteristics of Subjects

The baseline characteristics of the screened subjects are as summarised in Table 7.1. 1523 subjects (93%) had a determination of the ACE I/D polymorphism made.

Table 7.1: Characteristics of the population

		Screened Population (n=1640)	Subjects with a measured Ejection Fraction (n=1467)
Age	mean (SD) range	50.8(14) 25-74	50.4(14.1) 25-74
Sex	males	48.6%	48.3%
Self reported angina		9.8%	9.5%
Self reported MI		5.2%	5.1%
Diabetes		3.1%	2.7%
Hypertension		31.8%	30.7%
SBP(mmHg)	mean(SD)	133(23)	133(23)
DBP(mmHg)	mean(SD)	78(12)	78(12)
Body Mass Index (kg/m^2)	mean(SD)	26.2(4.9)	26.0(4.3)
Cholesterol (total) mg/ml	mean(SD)	6.07(1.23)	6.07(1.24)

7.3.2 Distribution of ACE genotypes

The distribution of the DD, ID and II genotypes in the screened population was 28.4 per cent, 48.2 per cent and 23.4 per cent respectively. There was an overall frequency of 52.5 per cent for the D allele and 47.5 per cent for the I allele. This genotype distribution was not significantly different from that assuming Hardy-Weinberg equilibrium and compares closely with that of other white populations studied (Schunkert et al. 1994, Gardemann et al. 1995, Cambien et al. 1992, Mattu et al. 1995).

7.3.3 ACE Genotype and ECG evidence of IHD

Subjects were categorised according to the presence or absence of minor and major ECG abnormalities and ECG evidence of myocardial infarction as described in Chapter 2. This was possible in 1482 individuals. The ACE genotype frequencies in each of these patient categories is shown in Table 7.2. The D allele of the ACE deletion polymorphism was significantly more frequent in patients with a major ECG abnormality or ECG evidence of myocardial infarction, with an odds ratio for DD versus II of 1.53 (p=0.031).

7.3.4 ACE Genotype and LVEF in Patients With IHD

As anticipated, an association was found between ECG evidence of ischaemia/infarction and left ventricular ejection fraction (LVEF). Patients with ECG evidence of ischaemia/infarction, the majority of whom were over the median age of the population of 51 years, had a lower LVEF (Table7.3). (The association between LVEF and these ECG abnormalities was only significant for subjects > than the median age of 51 years).

Table 7.2 ACE Genotypes and ECG Evidence of IHD

ECG Category	ACE genotype		
	DD	ID	II
Normal	27% (337)	49% (599)	24% (293)
Minor	35% (7)	40% (8)	25% (5)
Major	33% (65)	49% (97)	19% (37)
MI	41% (14)	35% (12)	24% (8)
Major or MI	34% (79)	47% (109)	19% (45)

Legend to Table7.2 The D allele was significantly more frequent in subjects with a major ECG abnormality or ECG evidence of MI. (Odds Ratio: DD versus II of 1.53 and for ID versus II of 1.18, p=0.031 for trend.)

Table 7.3: LVEF in Patients With IHD

	<51 years	>51 years
ECG Category	Mean LVEF ±SD(n)	Mean LVEF±SD(n)
Normal	47.2%±6.8(601)	46.5%±7.7(502)
Minor	47.3%±4.0(3)	48.7%±5.6 (14)
Major	49.0%±8.5(35)	43.2%±12.2 (137)
MI	49.7%±4.4(8)	41.3%±11.7(23)

Legend to Table 7.3 The association between and ECG major/MI categories and LVEF% was significant at $p<0.0001$ in subjects age>51 years.

An association was also found between the ACE gene polymorphism and LVEF in patients with ECG evidence of IHD (Table 7.4). The average LVEF in patients with the D allele was significantly higher than in II homozygotes ($p<0.02$). Significantly fewer patients with the D allele had severely depressed left ventricular function (i.e. LVEF <35% or LVEF <30%) (Table 7.4).

7.3.5 ACE Genotype, LVEF and Left Ventricular Dimensions

In support of the above findings, DD homozygotes with reduced ejection fractions had smaller left ventricular dimensions. For example, mean left ventricular diastolic dimension in ischaemia/infarction subjects with the DD genotype was 4.93 cm whereas it was 5.64 cm in II homozygotes (Table 7.5).

7.3.6 ACE Genotype, Systolic Blood Pressure and LVEF

The relationship between systolic blood pressure, the ACE I/D polymorphism and LVEF is shown in Table 7.6. LVEF was higher in older subjects (age > median) with a higher systolic blood pressure (> median) who had the D allele. Subjects of this type who had the DD genotype had a mean LVEF of 47.5 per cent compared to those with the II genotype who had a mean LVEF of 44.6 per cent ($p=0.012$). This relationship was found both in subjects with a normal ECG ($P<0.04$) and in those with ECG evidence of ischaemia/infarction ($p<0.03$) (Table 7.7). Subjects homozygous for the I allele, with a higher systolic blood pressure and an abnormal ECG, had the lowest LVEF (mean 41.0 per cent compared to 47.6 per cent in those who were DD genotype and had a lower blood pressure and normal ECG).

Table 7.4 :

LVEF According to ACE Genotype in Subjects With ECG Evidence of Major Ischaemia / Infarction

	ACE genotype		
	DD	ID	II
LVEF (mean ±SD)	44.6 (12.2)	42.9 (11.5)	40 (13.1)
Subjects with LVEF<30%	4 (7%)	7 (9%)	7 (24%)
Subjects with LVEF<35%	9 (16%)	15 (20%)	7 (24%)

Legend to Table 7.4 Effect of ACE I/D genotype on LVEF, $p<0.02$, effect of ECG ischaemia or infarction on LVEF, $p<0.0002$. The interaction between the ACE genotype and ECG/ischaemia and infarction was NS. Subjects were all >51 years, n=556.

Table 7.5

ACE Genotype, Left Ventricular Ejection Fraction and Left Ventricular Dimensions in Subjects With Reduced Left Ventricular Ejection Fraction (LVEF <0.30)

		Genotype		
LVEF≤30%		DD	ID	II
Absent	LVESD (cm)	3.35	3.34	3.37
Absent	LVEDD (cm)	4.94	4.94	5.01
Present	LVESD (cm)	3.58	3.64	4.30
Present	LVEDD (cm)	4.93	5.50	5.64

Legend to Table 7.5.

ACE I/D: effect on (LVESD) $p<0.007$

effect on (LVEDD) $p<0.01$

The analysis refers to the 958 individuals with a LVEF< M-Mode echocardiogram and ACE I/D type.

Table 7.6

ACE Genotype, Systolic Blood Pressure and LVEF In all Subjects >51 Years

	Mean LVEF ±SD(n)	
	SBP>141mmHg*	SBP<141mmHg
DD (n)	47.5%± 8.3(56)	44%± 9.3(138)
ID (n)	45.8%± 9.6(107)	46%± 8.6(234)
II (n)	44.6%± 8.8(53)	46.6%± 9.9(106)

Legend to Table 7.6

SBP (systolic blood pressure)
* Median SBP for those >51 years =141 mm Hg

LVEF was significantly higher in subjects with a SBP >median value who had the D allele (p=0.012).

Table 7.7

ACE Genotype and LVEF in Subjects Over 51 Years With a Systolic Blood Pressure Greater Than the Median Value

	Normal ECG	ECG major ischaemia or MI
ACE genotype	LVEF Mean±SD (n)	LVEF Mean ±SD (n)
DD	47.6%±6.7(96)	47.1%±11.3 (42)
ID	46.4%± 8.7(181)	43.5%±11.8 (52)
II	45.4%± 7.6(85)	41.0%±12.3 (21)

Legend to Table 7.7

The association between the D allele and LVEF was significant at $p<0.04$ for subjects with a normal ECG and at $p<0.03$ for those with ECG evidence of major ischaemia or MI.

7.3.7 ACE Genotype and Left Ventricular Hypertrophy

No association was found between the ACE I/D polymorphism and left ventricular hypertrophy (LVH) (Table 7.8) in the 40 subjects with ECG criteria for LVH. Similarly there was no relationship between the ACE I/D status and echocardiographically measured left ventricular mass (Table 7.9) in the 1118 subjects with this measurement available. The known effect of gender on left ventricular mass was, however, identified (Table 7.9).

Table 7.8

ACE Genotype and Electrocardiographic Left Ventricular Hypertrophy

	%LVH (n)		
	Men	Women	All
DD	3.1(2)	1.0 (2)	2.1(4)
ID	5.5(19)	1.9(7)	3.6(26)
II	4.3(7)	1.6(3)	2.9(10)

Legend to Table 7.8

LVH denotes left ventricular hypertrophy.

No significant differences were detected between the % of LVH and ACE I/D type.

Table 7.9

ACE Genotype and Echocardiographic Left Ventricular Mass

	LV Mass (g, mean±SEM)	
	Men	**Women**
DD	154.7 (3.6)	130.4 (3.3)
ID	150.1 (2.6)	134.3 (2.4)
II	154.6 (3.6)	129.2 (3.1)

Legend to Table 7.9

The effect of gender on LV mass was significant at $p<0.0001$. The analysis refers to the 1118 individuals with this measurement available.

7.4 DISCUSSION

The study has a number of significant findings. It confirms, in a large cross sectional population survey, the association between the ACE I/D polymorphism and ischaemic heart disease, whereby the prevalence of ECG evidence of ischaemia or infarction is greater in subjects with the D allele (Gardemann et al. 1995, Cambien et al. 1992, Mattu et al. 1995, Samani et al. 1996, Nakauchi et al. 1996). A novel and important additional finding is the association between the ACE I/D polymorphism and left ventricular ejection fraction (LVEF). LVEF was higher in older subjects with the D allele who had ECG evidence of ischaemia or infarction compared to similar patients who possessed the II genotype. Similarly, it was found that possession of the D allele was associated with a higher LVEF in older subjects, with a systolic blood pressure above the population median. Each of these main findings is worthy of discussion.

In their original case control study, Cambien et al reported an increased frequency of the ACE gene D allele in patients with myocardial infarction (odds ratio DD versus II 1.34) (Cambien et al. 1992). Of a large number of subsequent studies, the majority, but not all, (Lindpainter et al. 1996) have confirmed this association between the ACE I/D and polymorphism and the prevalence/incidence of myocardial infarction (and, also the prevalence and extent of coronary artery disease) (Gardemann et al. 1995, Cambien et al. 1992, Mattu et al. 1995, Samani et al. 1996, Nakauchi et al. 1996). This study adds further evidence in favour of this association.

A more novel finding is the relationship of the ACE I/D polymorphism to left ventricular function, in patients with myocardial ischaemia/infarction. Left ventricular systolic dysfunction, characterised by a reduction in LVEF, is a common complication of myocardial infarction (MI). Left ventricular systolic dysfunction may be immediately apparent after MI or may develop over time through a process referred to as remodelling. The results show that LVEF was higher in subjects with myocardial ischaemia/infarction and the D allele. Specifically, mean LVEF in older subjects with ECG evidence of infarction was 44.6% in DD homozygotes compared to 40.0% in those with the II genotype. An ejection fraction difference of 4.6 percentage points is of potentially great prognostic significance (The Multicentre Post Infarction Research Group, 1983, Cintron et al. 1993). The proportion of subjects with a significantly reduced ejection fraction (LVEF <30%) in each of these two groups was 7% versus 24% respectively. These findings are supported by the observation that DD homozygotes have significantly smaller left ventricular end systolic and end diastolic dimensions.

These results are possibly surprising in that subjects with the D allele might be expected to have been at greater risk of multiple infarction and, therefore, to have a *lower* LVEF. Similarly, it has been widely suggested that activation of the blood renin angiotensin system contributes to the decline of the LVEF in patients with LV dysfunction in a number of ways, including through alteration of ventricular loading conditions (Rouleau et al. 1993). Indeed, two short term serial follow-up studies after infarction have shown that survivors with the DD genotype were more likely to show ventricular dilation and a fall in

LVEF (Ohmichi et al. 1995, Pinto et al. 1995). Why this cross-sectional population survey reveals different findings from those serial studies in cases is not clear. One possibility is that there has been selective loss, through premature mortality, of low ejection fraction patients with the DD genotype. This would be in keeping with the existing observations outlined above, suggesting a detrimental cardiovascular effect of this genotype.

On the other hand, the higher mean ejection fraction in the DD genotype groups may reflect a beneficial effect of the D allele on myocardial structure and function. Preservation of left ventricular systolic function and volume after myocardial infarction may depend on an adequate myocardial hypertrophic response. One of the characteristic changes following infarction is hypertrophy of the non-infarcted myocardium (Gaudron and et al, 1992). This is believed to limit or halt progressive remodelling by reducing or normalising left ventricular wall stress (wall stress is believed to be the major stimulus for the remodelling process). The blood renin angiotensin system and the ACE genotype D allele both appear to facilitate hypertrophy of the human left ventricle (Harrap et al. 1996, Schunkert et al. 1994, Danser et al. 1995, Montgomery, 1996). For example, DD homozygotes show an increased myocardial hypertrophic response in hypertension (in some studies) (Schunkert et al. 1994, Rouleau et al. 1993, Abraham et al. 1995) and in response to exercise training (Montgomery et al. 1997). There is evidence from the pulmonary circulation to support this theory: patients with pulmonary hypertension who have the DD genotype have maintained cardiac

outputs and less right heart failure than those who are non-DD (Abraham et al. 1995).

Despite the attractiveness of this theory, no significant association between the ACE I/D polymorphism and left ventricular mass in the subjects studied could be found. This lack of association could be real or could reflect a number of confounding factors. Firstly and most importantly, it was not possible to make an accurate assessment of LV mass in a large proportion of subjects. Disease and treatment factors also confound any analysis. Distortion of the normal LV spherical geometry by infarction invalidates the assumptions on which the calculation of LV mass is made. LV mass also increases after infarction. Anti-hypertensive therapy can reduce LV mass. These factors may have obscured a real association between LV mass and the ACE I/D polymorphism.

Alternatively, therefore, it could simply be that DD homozygotes generate more myocardial angiotensin II with its positive inotropic action (Foult et al. 1988, Schomish et al. 1990). Either of these explanations would also fit with the relationship between LVEF and systolic blood pressure we also found and which is described below. There is, however, a third possible explanation for the findings in post-infarct survivors. After infarction, ACE activity increases in the infarcted segment of the myocardium and is believed to contribute to the development of a fibrous scar (Weber et al. 1995). Ability to rapidly lay down a rigid scar may lessen infarct segment expansion and ventricular dilation. Patients with the DD genotype may be better able to do this.

Other studies in patients with heart failure do not help in determining whether the DD genotype is detrimental or protective with respect to myocardial function. Raynolds et al, reported a greater prevalence of the ACE DD genotype amongst patients with end stage heart failure than in a normal control group (Raynolds et al. 1993). Whilst this has been interpreted as indicating that the DD genotype predisposes to myocardial failure, it is also possible that the DD genotype confers a survival advantage in these circumstances, i.e. these patients with advanced heart failure, undergoing transplantation, are selected survivors from the general population of patients with heart failure. Furthermore, other studies do not support an association between the ACE I/D polymorphism and heart failure (Sanderson et al. 1996, Andersson and Sylven, 1996, Montgomery et al. 1995). However, one recent study suggests that patients with heart failure, who have the DD genotype, have a worse prognosis (Andersson and Sylven, 1996).

This study also found that subjects who were homozygotes for the D allele had a higher LVEF in the face of higher systolic blood pressures. As is the case following myocardial infarction, the heart's ability to preserve systolic function as blood pressure increases depends on its ability to hypertrophy. In older subjects with a normal ECG and a high systolic arterial pressure, mean LVEF was 47.6% in DD homozygotes versus 45.4% in those with the II genotype. In similar subjects with an ECG indicative of myocardial ischaemia/infarction, mean LVEF was 47.1% and 41.0%, respectively. These findings lend support to the observations in patients with ECG evidence of infarction and one interpretation, discussed above. They are

also consistent with the recently reported observations of Montgomery et al. (Montgomery et al. 1997). These authors have shown that the DD genotype results in greater exercise training induced left ventricular hypertrophy in healthy young male adults. In other words, it seems that the ACE I/D polymorphism may modulate the common hypertrophic response to three separate stimuli to hypertrophy, i.e. infarction, hypertension and exercise training.

In summary these findings raise the intriguing possibility that the ACE I/D polymorphism has a bi-directional effect in coronary heart disease. The DD genotype may predispose to infarction but may also protect the left ventricle from the insult of infarction or hypertension, at least in the short to medium term. The true effect of the ACE I/D polymorphism on myocardial structure and function deserves further investigation.

Chapter 8

General Discussion

The data presented in this thesis provides some novel information on the epidemiology of left ventricular systolic dysfunction in a typical, urban population in an industrialised society and raises some important issues of how best to detect it. Before summing up the major findings and their implications both for future research and clinical practice, it is necessary to discuss the definition of left ventricular systolic dysfunction used throughout.

Crucial to any discussion on the prevalence of a condition is the premise on which its presence or absence is decided, in this case how to define abnormal left ventricular function according to the left ventricular ejection fraction.

The method employed to detect left ventricular systolic dysfunction in this population-based study had to be non invasive. The left ventricular ejection fraction was chosen as it is a parameter of left ventricular systolic performance with both clinical and prognostic significance (Murray et al. 1974, Nelson et al. 1975) . It was also the index of left ventricular function used to recruit patients in the majority of the heart failure treatment and post MI ventricular dysfunction trials (which have vindicated the use of the angiotensin converting enzyme inhibitors as effective in reducing morbidity and mortality in CHF and asymptomatic left ventricular systolic dysfunction). It would not have been desirable to expose the general public to radiation, which ruled out the use of radionuclide ventriculography which does provide a more reproducible measure of left ventricular ejection fraction (Ray et al. 1995). In addition, echocardiography is a powerful investigative tool, is more widely available in hospitals in the UK than radionuclide ventriculography (Ray et al. 1995), and provides more information than radionuclide methods regarding

the possible aetiology of left ventricular systolic dysfunction by its ability to interrogate valve function and wall motion. In this study the most accurate biplane method of assessing LVEF, that which correlates best with both angiographic and radionuclide measurements (Stamm et al. 1992) and the one which is most valid to use in the presence of a wall motion abnormality (Albin and Rahko, 1990) was used. The measurement was made meticulously, using the same scanning equipment and the same sonographer in two thirds of the studies. The conversion of the images to figures was done by a single analyser, making measurements in triplicate. The interobserver and intraobserver variation were similar to, or superior than, other echocardiographic studies.

Unfortunately, there are no published echocardiographic population studies using this particular method available to us for comparison. Normal ranges cited in textbooks etc. are based on small samples of healthy volunteers. Defining abnormality could be likened, to some extent, as trying to define high or low blood pressure. Essentially there are two approaches. The first is to define "statistical" abnormality, taking any LVEF more than two standard deviations from the mean as abnormal and the second is to try and predict "biological" abnormality. The statistical approach would give a cut-off point of approximately 35%. It would also, however, almost certainly include some biologically normal people, not least because of the problem of regression to the mean. The strength of this study lies in the collection of other important information allowing the determination, with reasonable certainty, as to whether or not the "abnormal" LVEF subjects were really *biologically*

abnormal. From the clinical history and ECG it is known whether or not the subjects had a reason to have systolic dysfunction. In addition there is physiological data to show whether or not there has been a *compensatory response* to a reduction in left ventricular function i.e. a rise in blood natriuretic peptide concentrations. Similarly, there is physiological information to tell us whether there has been a *functional consequence* of left ventricular impairment i.e. a reduction in exercise tolerance. Taking all of these data it is clear that the cut-off point for a *biologically* abnormally low LVEF is more like 30% than 35%. Although, it is acknowledged earlier that the lower limit of normal could be considered to lie in the range 30-35%.

It should be stressed that quantitative imaging of the heart by any modality leads to variation in the result obtained between observers, and within observers (Baur et al. 1996). It has become increasingly apparent (and this study lends added weight to this point) that values of the left ventricular ejection fraction below which left ventricular systolic dysfunction is diagnosed should be interpreted in the light of the normal range for the centre (Ray et al. 1995). This will vary with the echocardiographic equipment used to acquire the images, the operator, the analyser and the software package and geometric formulae which are used for the particular calculation chosen. This study strove to produce optimal conditions for the derivation of ejection fraction in this population. It is accepted that this value is not applicable to other centres. It is, however, *abnormal* for *this population* using *this method.*

It is also worth pointing out that the cut-off point for abnormal used in this study is not dissimilar from that in the largest clinical trial in heart failure and

asymptomatic left ventricular systolic dysfunction (SOLVD) i.e. 35% (The SOLVD Investigators, 1991, The SOLVD Investigators, 1992). This is important as a) the method used in this work for measuring LVEF gives similar values to radionuclide ventriculography (Stamm et al. 1992) (the most common method used in SOLVD) and b) 21% of patients were randomised into SOLVD on the basis of an echocardiographic LVEF of ≤35% (The SOLVD Investigators, 1991); in SOLVD, RNVG or echocardiography were equally predictive of outcome. Indeed, in SOLVD, the major benefit of enalapril was in patients with a LVEF<30%. Those in the range 30-35% obtained little, if any benefit (The SOLVD Investigators, 1992). Having given some consideration to the "gold standard" used to detect left ventricular systolic dysfunction, it is now possible to outline the significance of the abnormalities detected.

The results presented in Chapter Three established that left ventricular systolic dysfunction is common. Moreover, they uncovered the fact that, at least half of that dysfunction is asymptomatic. The findings presented in Chapter Four confirmed the generally held view that the major aetiological correlate of left ventricular systolic dysfunction in the 1990s is ischaemic heart disease. This chapter also drew attention to the association of hypertension with left ventricular systolic dysfunction, especially in the presence of ischaemic heart disease. It also began to answer the question of the importance of the asymptomatic left ventricular systolic dysfunction which had been discovered, in that the majority of these subjects had prevalent ischaemic heart disease or hypertension, suggesting that they have disease

similar to the patients in the SOLVD Prevention Trial who derived benefit from ACE inhibition (The SOLVD Investigators, 1992). The work outlined in Chapter Five added to the hypothesis that the left ventricular systolic dysfunction identified was biologically important in that it caused a significant impairment of effort capacity. Chapter Six extended this finding to confirm that both the symptomatic and asymptomatic left ventricular systolic dysfunction identified was associated with a compensatory physiological response i.e. raised circulating concentrations of the natriuretic peptide hormones. In addition the natriuretic peptides, particularly BNP, were shown, for the first time, to have acceptable accuracy to be used in the detection of both symptomatic and asymptomatic left ventricular systolic dysfunction in the general population. The results detailed in Chapter Seven, whilst confirming an association of the ACE I/D polymorphism with IHD, provided a novel finding of the DD genotype seeming to confer a more favourable ejection fraction especially in those groups, shown earlier to be at high risk of left ventricular systolic dysfunction, leading to the mechanistic speculation that the DD genotype may allow more advantageous remodelling post myocardial infarction.

All of these findings have implications for future research and clinical practice. Several studies require to be carried out as a result of this work. Firstly, rescreening of the population by similar methods to establish the incidence of left ventricular systolic dysfunction and to answer the crucial question of whether the asymptomatic left ventricular systolic dysfunction identified does indeed progress to symptomatic left ventricular systolic dysfunction. This

study is now underway in the MRC CRI in Heart Failure (University of Glasgow). It will also, provide information on the predictive role of the natriuretic peptides in determining prognosis. Further work is also needed to test the usefulness of BNP in detecting LV systolic dysfunction by testing its use in the high risk groups identified in this study i.e. breathless subjects and those with IHD and hypertension, to ascertain its cost-effectiveness. From the more mechanistic genetic findings, it would be valuable to test the hypothesis further by utilising a treatment with an emerging role in CHF i.e. exercise prescription. It may be that subjects with CHF who are also DD may benefit from exercise training.

This research also has important bearings on clinical practice. We are all too well aware that the syndrome of CHF is an important medical problem. By the time it is diagnosed on clinical grounds, as well as being associated with much morbidity, it has a mortality which exceeds that of many common cancers (Swedberg et al. 1987,The SOLVD Investigators, 1991). This research has highlighted that symptomatic left ventricular systolic dysfunction is common. Moreover, it has ascertained that its asymptomatic precursor, is just as common. The left ventricular systolic dysfunction identified was underdiagnosed and undertreated. It also existed in certain well defined clinical groups. BNP was also shown to have acceptable sensitivity and specificity to detect the systolic dysfunction. As a result of the information which has accrued over the last decade that ACE inhibitors reduce both morbidity and mortality in CHF and asymptomatic left ventricular systolic dysfunction i.e. there is effective treatment currently available (and with

several other therapeutic options, including beta blockers and angiotensin II type 1 receptor antagonists looking promising). These four points fulfil the first of the five principles required for screening for a disease (Wilson and Junger, 1968, Rose and Barker, 1986). The fifth is that screening should be cost-effective. This is more complex to define and depends on a number of factors including the cost of the test and the efficacy of the available treatment. Currently a BNP assay costs a fraction of that of an echocardiogram. Rapid, more user-friendly and cheaper assays are nearly available. In terms of other cardiovascular therapies, ACE inhibitors are very cost effective treatments for heart failure (McMurray and Davie, 1996), principally due to their effect in reducing hospitalisation. Formal analysis of the SAVE study also showed them to be cost effective as treatments for post MI asymptomatic LV dysfunction (Tsevat et al. 1995). These reasons suggest that any screening programme for left ventricular systolic dysfunction is likely to be cost effective. The ability to identify high risk subgroups is also an important consideration in terms of the overall cost. It is worth emphasising that the antecedents of left ventricular systolic dysfunction lie in easily identified high risk subgroups (hypertensives, post infarct subjects, those with angina and diabetics and the elderly). By comparison, 160 women aged 45-64 years would have to be screened by mammography to detect one single true breast carcinoma and as many as 40,000 cervical smears and 200 cone biopsies may be necessary to prevent one death due to cervical cancer (Wilson, 1991).

A programme to detect and treat symptomatic left ventricular systolic dysfunction and to screen for and treat asymptomatic left ventricular systolic dysfunction does seem to fulfil all five principles of screening. This work has placed the question of screening for asymptomatic, and detection of symptomatic, left ventricular systolic dysfunction firmly on the agenda.

REFERENCES

Abraham, W.T., Raynolds, M.V., Gottschall, B., et al. Importance of angiotensin-converting enzyme in pulmonary-hypertension. *Cardiology* 1995;**86**:9-15.

Ahnve, S., Eggersten, G., Hot-Bjelak, A., et al. Angiotensin converting enzyme gene polymorphism and acute myocardial infarction. *Eur Heart J* 1995;**16**:(Suppl):P468.

Akhras, F., Jackson, G. Raised Exercise Diastolic Blood Pressure as Indicator of Ischaemic Left Ventricular Dysfunction. *Lancet* 1991;**337**:899-900.

Albin, G., Rahko, P.S. Comparison of echocardiographic quantitation of left ventricular ejection fraction to radionuclide angiography in patients with regional wall motion abnormalities. *Am. J. Cardiol.* 1990;**65**:1031-1032.

Andersson, B., Sylven, C. The DD genotype of the angiotensin-converting enzyme gene is associated with increased mortality in idiopathic heart failure. *Journal of the American College of Cardiology* 1996;**28**:162-167.

Baker, K.M., Aceto, J.F. Angiotensin II stimulation of protein synthesis and cell growth in chick cells. *Am J Physiol* 1990;**259**:H610-H618.

Baur, L.H.B., Schipperheyn, J.J., Van Der Velde, E.A., et al. Reproducibility of left ventricular size, shape and mass with echocardiography, magnetic resonance imaging and radionuclide angiography in patients with anterior wall infarction. *International Journal of Cardiac Imaging* 1996;**12**:233-240.

Benjamin, E.J., Levy, D., Anderson, K.M., et al. Determinants of Doppler indexes of left ventricular diastolic function in normal subjects (the Framingham Heart Study). *Am. J. Cardiol* 1992;**70**:(508):515

Berning, J., Nielsen, J.R., Launbjerg, A., et al. Rapid estimation of left ventricular ejection fraction in acute myocardial infarction by echocardiographic wall motion analysis. *Cardiology* 1992;**80**:257-266.

Bohn, M., Berge, K., Bakken, A., et al. Insertion/deletion (I/D)polymorphism at the locus for angiotensin 1 converting enzyme and myocardial infarction. *Clin Genet* 1993; **44**:292-297.

Bonarjee, V.V.S., Omland, T., Nilsen, D.W.T., et al. Left ventricular volumes, ejection fraction, and plasma proatrial natriuretic factor (1-98) after withdrawal of enalapril treatment initiated early after myocardial infarction. *British Heart Journal* 1995;**73**:506-510.

Bonneaux, L., Barendregt, J.J., Meeter, K., et al. Estimating clinical morbidity due to IHD and congestive heart failure: the future risk of heart failure. *Am J Public Health* 1994;**84**:20-28.

Bounous, E.P., Mark, D.B., Pollock, B.G., et al. Surgical survival benefits for coronary disease patients with left ventricular dysfunction. *Circulation* 1988;**78**:I151-7.

Bourassa, M.G., Gurne, O., Bangdiwala, S.I., et al. Natural history and patterns of current practice in heart failure. *J Am Coll. Cardiol* 1993;**22**:(4):14A-19A.

Braunwald, E. 1997; Pathophysiology of Heart Failure. In: Saunders, W.B. (Ed.) *Heart Disease*, **5th**:pp. 394-420. Philadelhpia: Saunders,W.B.

Buikema, H., Pinto, Y.M., Rooks, G., et al. The deletion polymorphism of the angiotensin-converting enzyme gene is related to phenotypic differences in human arteries. *European Heart Journal* 1996;**17**:787-794.

Califf, R., Bengtson, J. Cardiogenic Shock. *N Engl J Med* 1994;**330**(24):1724-1730.

Cambien, F., Poirier, O., Lecerf, L., et al. Deletion polymorphism in the gene for angiontensin-converting-enzyme is a potent risk factor for myocardial infarction. *Nature* 1992;**359**:641-643.

Cambien, F., Costerousse, O., Tiret, L., et al. Plasma level and gene polymorphism of angiotensin converting enzyme in relation to myocardial infarction. *Circulation* 1994;**90**:669-676.

Choy, A.M., Darbar, D., Lang, C.C., et al. Detection of left ventricular dysfunction after acute myocardial infarction: Comparison of clinical, echocardiographic, and neurohormonal methods. *British Heart Journal* 1994;**72**:16-22.

Cintron, G., Johnson, G., Francis, G., et al. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. *Circulation* 1993;**87**:VI17-VI23.

Clarke, K.W., Gray, D., Hampton, J.R. How common is heart failure?. Evidence from PACT(Prescribing Analysis and Cost) data in Nottingham. *J Public Health Medicine* 1995;**17**:459-464.

Clarkson, P.B.M., Whelldon, N.M., MacFadyen, R.J., et al. Effects of brain natriuretic peptide on exercise hemodynamics and neurohormones in isolated diastolic heart failure. *Circulation* 1996;**93**:2037-2042.

Cody, R.J., Atlas, S.A., Laragh, J.H., et al. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. *J Clin. Invest.* 1986;**78**:1362-1374.

Cohn, J.N., Archibald, D.G., Ziesche, S., et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547-1552.

Cohn, J.N., Johnson, G., Ziesche, S., et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of patients with chronic congestive heart failure. *N Engl J Med* 1991;**325**:(5):303-310.

Cohn, J.N., Johnson, G.R., Shabetai, R., et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**:VI5-16.

Cohn, J., Johnson, G. The Ve-HeFT Study. *Circulation* 1990;**81**:(Suppl 111):48-53.

Costanzo, M.R., Chair, S.A., Borge, R., et al. Selection and treatment of candidates for heart transplantation. *Circulation* 1995;**92**:3593-3612.

Costerousse, O., Allegrini, J., Lopez, M., Alhenc-Gelas, F. Angiotensin-I-converting enzyme in human circulating mononuclear cells; genetic polymorphism of expression in T-lymphocytes. *Biochem J* 1993;**290**:33-34.

Danser, A.H.J., Schalekamp, M.A.D.H., Bax, W.A., et al. Angiotensin-converting enzyme in the human heart - effect of the deletion insertion polymorphism. *Circulation* 1995;**92**:1387-1388.

Davidson, N.C., Coutie, W.J., Struthers, A.D. N-terminal proatrial natriuretic peptide and brain natriuretic peptide are stable for up to 6 hours in whole blood in vitro. *Circulation* 1995;**91**:1276-1277.

Davis, M., Espiner, E., Richards, G., et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;**343**:440-444.

Devereux, R.B., Manse, D.R., Lutas, E.M. Echocardiographic assessment of left ventricular hypertrophy:comparison with necropsy findings. *Am J Cardiol* 1986;**57**:450-458.

Dinkel, R., Buchner, K., Holtz, J. Chronic heart failure:Socioeconomic relevance in the Federal Republic of Germany. *Munsch. Med. Wshr* 1989;**131**:689-699.

Dougherty, A.H., Nacarelli, G.V., Gray, E.L., et al. Congestive heart failure with normal systolic function. *Am J Cardiol* 1984;**54**:778-782.

Dubin, J., Wallerson, D., Cody, R., Devereux, R. Comparative accuracy of doppler echocardiographic methods for clinical stroke volume determination. *American Heart Journal* 1990;**120**:116-123.

Eriksson, H., Svardsudd, K., Larsson, B., et al. Quality of life early heart failure. The study of men born in 1913. *Scandinavian Journal of Primary Health Care* 1988;**6**:161-167.

Eriksson, H., Svardsudd, K., Larsson, B., et al. Risk factors for heart failure in the general population: the study of men born in 1913. *European Heart Journal* 1989;**10**:647-656.

Evans, A., Poirer, O., Kee, F. Polymorphisms of the angiotensin converting enzyme gene in subjects who die from coronary heart disease. *Q J Med* 1994;**87**:211-215.

Fahey, M.T., Irwig, L., Macaskill, P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;**141**:680-689.

Fletcher, C.M., Elmes, P.C., Fairbairn, A.S., Wood, C.H. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959;**5147**:257-266.

Folland, E.D., Parisi, A.F., Moynihan, P.F., et al. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. *Circulation* 1979;**60**:(4):760-766.

Foult, J.M., Tavolaro, I., Antony, I., Nitenberg, A. Direct myocardial and coronary effects of enalaprilat in patients with dilated cardiomyopathy: assessment by a bilateral intracoronary infusion technique. *Circulation* 1988;**77**:337-344.

Franciosa, J.A., Ziesche, S., Wilen, M. Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and hemodynamic characterization. *American Journal of Medicine* 1979;**67**:460-466.

Franciosa, J.A., Park, M., Levine, T.B. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol* 1981;**47**:33-39.

Francis, G.S., Benedict, C., Johnstone, D.E., et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990;**82**:1724-1729.

Froelicher, V.F. 1994. *Manual of Exercise Testing.* 2nd edition: St Louis.Missouri. Mosby-Year Book Inc.

Galderisi, M., Lauer, M.S., Levy, D. Echocardiographic determinants of clinical outcome in subjects with coronary artery disease (The Framingham Study). *Am. J. Cardiol* 1992;**70**:(11):971-976.

Gardemann, A., Weib, T., Schwartz, O., et al. Gene polymorphism but not catalytic activity of angiotensin 1-converting enzyme is associated with coronary artery disease and myocardial infarction in low-risk patients. *Circulation* 1995;**92**:(10):2796-2799.

Gardin, J.M., Siscovick, D., Anton-Culver, H., et al. Sex, Age, and Disease Affect Echocardiographic Left Ventricular Mass and Systolic Function in the Free-Living Elderly. The Cardiovascular Health Study. *Circulation* 1995;**91**:(6):1739-1748.

Gaudron, P., et al. Compensatory and non-compensatory left ventricular dilation after myocardial infarction:time course, haemodynamic consequences at rest and exercise. *Am Heart J* 1992;**123**:377-385.

Geenen, D.L., Malhotra, A., Scheur, J. Angiotensin II increases cardiac protein synthesis in adult rat heart. *Am J Physiol* 1990;**265**:H238-H243

Ghali, J.K., Cooper, R., Ford, E. Trends in hospitalization rates for heart failure in the United States, 1973-1986. Evidence for increasing population prevalence [see comments]. *Arch. Intern. Med.* 1990;**150**:769-773.

Gibson, T.C., White, K.L., Klainer, L.M. The prevalence of congestive heart failure in two rural communities. *J Chronic. Dis.* 1966;**19**:141-152.

Gillum, R.F. Heart Failure in the United States 1970-1985. *Am. Heart J.* 1987;**113**:(4):1043-1045.

Glenbotski, C.C., Dixon, J.E., Gibson, T.R. Secretion of atrial natriuretic factor(1-98) by primary cardiac myocytes. *J Biol Chem* 1988;**263**:16073-16081.

Gorkin, L., Norvell, N., Rosen, R.C., for the SOLVD Investigators. Assessment of quality of life as observed at baseline data of the Studies of Left Ventricular Dysfunction (SOLVD) Trial quality of life substudy. *Am J Cardiol* 1993;**71**:1069-1073.

Gottlieb, S.S., Kukin, M.L., Ahern, D., Packer, M. Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. *Journal of the American College of Cardiology* 1989;**13**:1534-1539.

Gregor, P., Widimsky, P., Cervenka, V., et al. Two-dimensional echocardiography in evaluating left ventricular function. *Cor Vasa* 1984;**26**:(1):1-11.

Hanley, J.A., McNeill, B.J. The meaning and use of the area under a receiver operator characteristic (ROC) curve. *Radiology* 1982;**143**:29-36.

Harrap, S., Davidson, R., Connor, M., et al. The angiotensin 1 converting enzyme gene and predisposition to high blood pressure. *Hypertension* 1993;**21**:455-460.

Harrap, S., Dominiczak, A., Fraser, R., et al. Plasma angiotensin II, predisposition to hypertension, and left ventricular size in healthy young Adults. *Circulation* 1996;**93**:(6):1148-1154.

Harris, P. 1987; Congestive heart failure: central role of the arterial blood pressure. *Br Heart J* **58**:190-203.

Heublein, D.M., Heser, D.W., Edwards, B.S., et al N-terminal (1-25) atrial natriuretic factor in human congestive heart failure: a marker for endogenous secretion. *J Am Coll Cardiol* 1989;**13**:9A

Ho, K.K., Anderson, K.M., Kannel, W.B., et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;**88**:107-115.

Ho, K.K., Pinsky, J.L., Kannel, W.B., Levy, D. The epidemiology of heart failure: the Framingham Study. *J. Am. Coll. Cardiol.* 1993;**22**:6A-13A.

Hubert, C., Houot, A.M., Corvol, P., Soubrier, F. Structure of the angiotensin 1 converting enzyme gene: two alternate promoters correspond to evolutionary steps of a duplicated gene. *J Biol Chem* 1991;**266**:15377-15383.

Hunt, P.J., Richards, A.M., Espiner, E.A., et al. Bioactivity and metabolism of C-type natriuretic peptide in normal man. *Journal of Clinical Endocrinology and Metabolism* 1994;**78**:1428-1435.

Jacobsen, S.J., Bergstralh, E.J., Guess, H.A., et al. Predictive properties of serum prostate-specific antigen testing in a community based setting. *Arch Inter Med* 1996;**156**:2462-2468.

Kangawa, K., Matsuo, H. Purification and complete amino acid sequence of alpha-human atrial natriuretic popypeptide (alpha-hANP). *Biochemical and Biophysical Research Communications* 1984;**118**:131-139.

Kannel, W.B., Sorlie, P., McNamara, P.M. Prognosis after initial myocardial infarction: the Framingham Study. *Am J Cardiol* 1979;**44**:53-59.

Kannel, W.B. Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J* 1987;**Suppl F**:23-26.

Kannel, W.B., Plehn, J.F., Cupples, L.A. Cardiac failure and sudden death in the Framingham Study. *Am Heart J* 1988;**115**:869-875.

Kinnunen, P., Vuolteenaho, O., Ruskoaho, H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: Effect of stretching. *Endocrinology* 1993;**132**:1961-1970.

Kitzman, D.W., Higginbotham, M.B., Cobb, F.R., et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism [see comments]. *J Am Coll. Cardiol* 1991;**17**:1065-1072.

Kober, L., Torp-Pedersen, C., Carlsen, J., et al. An Echocardiographic Method for Selecting High Risk Patients Shortly After Acute Myocardial Infarction, for Inclusion in Multi-Centre Studies (as used in the TRACE Study). *European Heart Journal* 1994;**15**:1616-1620.

Kober, L., Torp-Pedersen, C., Carlsen, J.E., et al. A clinical trial of the angiotensin-converting enzyme trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**327**:1670-1676.

Kohno, M., Horio, T., Yokokawa, K., et al. Brain natriuretic peptide as a cardiac hormone in essential hypertension. *American Journal of Medicine* 1992;**92**:29-34.

Kostis, J.B. The effect of enalapril on mortal and morbid events in patients with hypertension and left ventricular dysfunction. *Am J Hypertens* 1995;**8**:909-914.

Kreutz, R., Lindpainter, K., Pfeffer, M.A., et al. Angiotensin converting enzyme genotype and risk for coronary heart disease. *Circulation* 1993;**88**:1510

Kurtz, A., Della Bruna, R. Atrial natriuretic peptide inhibits renin release from juxtaglomerular cells by a cGMP mediated process. *Proc Natl Acad Sci USA* 1996;**83**:4769-4773.

Lang, C.C., Choy, A.M.J., Turner, K., et al. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. *Journal of Hypertension* 1993;**11**:737-741.

Lauer, M., Evans, J., Levy, D. Prognostic implications of subclinical left ventricular dilation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am. J. Cardiol.* 1992;**70**:1180-1184.

LeJemtel, T.H., Liang, C.S., Stewart, D.K., et al. Reduced peak aerobic capacity in asymptomatic left ventricular systolic dysfunction. A substudy of the studies of left ventricular dysfunction (SOLVD). *Circulation* 1994;**90**:(6):2757-2760.

Lenfant, C. Report of the Task Force on Research in Heart Failure. *Circulation* 1994;**90**:(3):1118-1123.

Lerman, A., Gibbons, R.J., Rodeheffer, R.J., et al. Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction [see comments]. *Lancet* 1993;**341**:1105-1109.

Levy, D., Larson, M.G., Vasan, R.S., et al. The progression from hypertension to congestive heart failure. *JAMA* 1996;**275**:(20):1557-1562.

Lindpainter, K., Lee, M.A., Larson, M.G., et al. Absence of association or genetic linkage between the angiotensin-converting enzyme gene and left ventricular mass. *N Engl J Med* 1996;**334**:1023-1028.

Lipkin, D.P., Perrins, J., Poole-Wilson, P.A. Respiratory gas exchange in the assessment of patients with impaired left ventricular function. *Br Heart J* 1985;**54**:321-328.

Ludwig, E., Cornell, P.S., Anderson, J.L., et al. The ACE insertion/deletion polymorphism is independently associated with myocardial infarction and body mass index but not with stenosis. *Circulation* 1993;**88**:I-364

Luscher, T. The Endothelium and Cardiovascular Disease - A Complex Relation. *N Engl J Med* 1994;**330**:(15):1081-1083.

Maggioni, A., Franzosi, M.G., Malacrida, R., Tognoni, G. Perspectives on Therapeutic Interventions in Patients with Acute Myocardial Infarction: Viewpoints After the GISSI-2 Results. *Clinical Cardiology* 1991;**14**:549-556.

Mair, F.S., Crowley, T.S., Bundred, P.E. Prevalence, aetiology and management of heart failure in general practice. *British Journal of General Practice* 1996;**46**:77-79.

Mancini, D.M., Eisen, H., Kussmaul, W., et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:(3):778-786.

Mancini, D.M., Walter, G., Reichek, N., et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure [see comments]. *Circulation* 1992;**85**:1364-1373.

Marcus, L.S., Hart, D., Packer, M., et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: A double- blind, placebo-controlled, randomized crossover trial. *Circulation* 1996;**94**:3184-3189.

Massie, B., Conway, M., Yonge, R., et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation* 1987;**76**:1009-1019.

Mathew, J., Davidson, S., Narra, L., et al. Etiology and characteristics of congestive heart failure in blacks. *Am J Cardiol* 1996;**78**:1447-1450.

Mattu, R.K., Needham, E.W.A., Galton, D.J., et al. A DNA variant in the angiotensin converting enzyme gene locus associates with coronary artery disease in the Caerphilly Heart Study. *Circulation* 1995;**91**:270-274.

McKee, P.A., Castelli, W.P., McNamara, P.M., Kannel, W.B. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441-1446.

McMahon, S., Hickey, A., Wilcken, D. M-Mode echocardiography: reproducibility of serial left ventricular measurements in subjects with normal ventricles and patients with congestive cardiomyopathy. *Aust NZ J Med* 1983;**13**:457-462.

McMurray,J. Ray, S.G., Abdullah,I., et al. Plasma endothelin in chronic heart failure. *Circulation* 1992;**85**:1374-1379.

McMurray, J., McDonagh, T., Morrison, C.E., Dargie, H.J. Trends in hospitalization for heart failure in Scotland 1980-1990. *Eur. Heart J* 1993;**14**:1158-1162.

McMurray, J., Davie, A. The pharmacoeconomics of ACE inhibitors in chronic heart failure. *Pharmacoeconomics* 1996;**9**:188-197.

McMurray, J., Hart, W. The Economic Impact of Heart Failure on the UK National Health Service. *European Heart Journal* 1993;**14**:(Supplement):P848

Meittinen, H., Korpela, K., Hamalainen, L., Kontula, K. Polymorphisms of the apoliprotein and angiotensin converting enzyme genes in young North Karelian patients with coronary heart disease. *Hum Genet* 1994;**94**:189-192.

Mitchell, G.F., Pfeffer, M.A. Left ventricular remodelling after myocardial infarction. p317. In Kloner RA (ed):The Guide to Cardiology.3rd edition.Le Jacq Communicatoins. New York 1995.

Montgomery, H. Renin-angiotensin system activity and myocardial hypertrophy:from rat to human. *Heart* 1996;**75**:

Montgomery, H.E., Keeling, P.J., Goldman, J.H., et al. Lack of association between the insertion/deletion polymorphism of the angiotensin-converting enzyme gene and idiopathic dilated cardiomyopathy. *J Am Coll. Cardiol* 1995;**25**:(7):1627-1631.

Montgomery, H.E., Clarkson, P., Dollery, C.M., et al. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation* 1997;**96**:741-747.

Mosterd, A., de Bruijne, M.C., Hoes, A.W., et al. Usefulness of echocardiography in detecting left ventricular dysfunction in population-based studies (the rotterdam study). *Am J Cardiol* 1997;**79**:103-104.

Motwani, J.G., McAlpine, H., Kennedy, N., Struthers, A.D. Plasma brain natriuretic peptide as an indicator for angiotensin-converting-enzyme inhibition after myocardial infarction [see comments]. *Lancet* 1993;**341**:1109-1113.

Moye, L.A., Pfeffer, M.A., Braunwald, E. Rationale and design of the Survival and Ventricular Enlargement Trial. *Am. J. Cardiol* 1989;**68**:70D-79D.

Mukoyama, M., Nakao, K., Saito, Y., et al. Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med* 1990;**323**:757-758.

Murdoch, D.R., Byrne, J., McDonagh, T.A., et al. BNP is stable in whole blood and can be measured using a simple rapid assay: implications for clinical practice. *Heart* 1997; **398**:594-597.

Murdoch, D.R., McDonagh, T.A., Morton, J.J., Dargie, H.J. Optimising the treatment of chronic heart failure : titration of vasodilator therapy according tp plasma brain natriuretic peptide concentration.
Eur Heart J. 1997;**18**:Suppl.

Murray, J.A., Chinn, N., Peterson, D.R. Influence of left ventricular function on early prognosis in atherosclerotic heart disease. *Am J Cardiol* 1974;**33**:159

Murray, L.J., Bamford, K.B., O'Reilly, D.P.J., et al. *Helicobacter Pylori* infection: relation with cardiovascular risk factors, ischaemic heart disease and social class. *Br Heart J* 1995;**74**:497-501.

Nakai, K., Itoh, C., Miura, Y., et al. Deletion polymorphism of the angiotensin 1 converting enzyme gene is asscociated with serum ACE concentration and increased risk for CAD in the Japanese. *Circulation* 1994;**90**:2199-2202.

Nakao, K., Ogawa, Y., Suga Si, Imura, H. Molecular biology and biochemistry of the natriuretic peptide system. I: Natriuretic peptides. *Journal of Hypertension* 1992;**10**:907-912.

Nakauchi, Y., Suehiro, T., Yamamoto, M., et al. Significance of angiotensin-1-converting enzyme and angiotensin II type 1 receptor gene polymorphisms as risk factors for coronary heart disease. *Atherosclerosis* 1996;**125**:161-169.

Nelson, N.B., Cohn, P.F., Garlin, R. Prognosis in medically treated coronary artery disease. Influence of ejection fraction compared to other parameters. *Circulation* 1975;**52**:408

Newby, D.E., McDonagh. T.A., Currie P.F et al. Candoxatril improves exercise capacity in patients with CHF receiving ACE Inhibition
J Am Coll Cardiol 1997;**29** (2); Suppl:7273.

Nicod, P., Gilpin,E., Dittrich,H. et al. Influence on prognosis and morbidity of left ventricular ejection fraction with and without signs of left ventricular failure after acute myocardial infarction. *Am J Cardiol* 1988;**61**:1165-1171.

Northridge, D.B., Grant, S., Henderson, E., et al. A novel exercise protocol suitable for use on a treadmill or bicycle ergometer. *Br Heart J* 1990;**64**:313-316.

Northridge, D.B., Jardine, A., Henderson, E., et al. Increased circulating atrial natriuretic factor concentrations in patients with chronic heart failure after inhibition of neutral endopeptidase: Effects on diastolic function. *British Heart Journal* 1992;**68**:387-391.

Ohmichi, N., Iwai, N., Nakamura, Y., Kinoshita, M. The genotype of the angiotensin-converting enzyme gene and global left ventricular dysfunction after myocardial infarction. *Am J Cardiol* 1995;**76**:326-329.

Omland, T., Aakvaag, A., Bonarjee, V.V.S., et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: Comparison with plasma atrial natriuretic peptide and N- terminal proatrial natriuretic peptide. *Circulation* 1996;**93**:1963-1969.

Omland, T., Aakvaag, A., VikMo, H. Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. *Heart* 1996;**76**:232-237.

Ossei-Gerning, N., Foy, C., Wilson, J., Grant, P. Angiotensin converting enzyme gene polymorphism and plasma levels in relation to the extent of coronary artery disease. *Eur Heart J* 1995;**16**:(Suppl):A-P472.

Packer, M. Survival in patients with chronic heart failure and its potential modification by drug therapy. In: Cohn, J. (Ed.) *Drug Treatment of Heart Failure*, **2nd**:pp. 323 Secaucus. N.J. ATC International.1988.

Parameshwar, J., Poole Wilson, P.A., Sutton, G.C. Heart failure in a district general hospital [see comments]. *J R. Coll. Physicians. Lond.* 1992;**26**:139-142.

Parameshwar, J., Shackell, M.M., Richardson, A., et al. Prevalence of heart failure in three general practices in north west London. *Br. J Gen. Pract.* 1992;**42**:287-289.

Perticone, F., Ceravolo, R., Cosco, C., et al. Deletion polymorphism of angiotensin-converting enzyme gene and left ventricular hypertrophy in southern italian patients. *Journal of the American College of Cardiology* 1997;**29**:365-369.

Pfeffer, M.A., Braunwald, E., Moye, L.A., et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators [see comments]. *N Engl J Med* 1992;**327**:669-677.

Pinto, Y.M., van Gilst, W.H., Kingma, J.H., Schunkert, H. Deletion-type allele of the angiotensin-converting enzyme gene is associated with progressive ventricular dilation after anterior myocardial infarction. *J. Am. Coll. Cardiol* 1995; **25**:(7):1622-1626.

Prineas, R.J., Crow, R.S., Blackburn, H. The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification. In: Anonymous Littleton, Mass. John Wright/PSG.1982.

Ray, S.G., Metcalfe, M.J., Oldroyd, K.G., et al. Do radionuclide and echocardiographic techniques give a universal cut off value for left ventricular ejection fraction that can be used to select patients for treatment with ace inhibitors after myocardial infarction? *British Heart Journal* 1995;**73**:466-469.

Raynolds, M., Bristow, M., Bush, E., et al. Angiotensin converting enzyme in patients with ischaemic or idiopathic dilated cardiomyopathy. *Lancet* 1993;**342**:1073-1075.

Remes, J., Reunanen, A., Aroma, A., Pyorala, K. Incidence of heart failure in Eastern Finland: a population based surveillance study. *Eur Heart J* 1992;**13**:583-593.

Rigat, B., Hubert, C., Alhenc-Gelas, F., et al. An insertion/deletion polymorphism in the angiotensin-1-converting enzyme gene accounting for half of the variance of serum enzyme levels. *J Clin Invest* 1990;**86**:1343-1346.

Rigat, B., Hubert, C., Corvol, P., Soubrier, F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCPI). *Nucleic Acid Res* 1992;**20**:1433

Riley, M., Northridge, D.B., Henderson, E., et al. The use of an exponential protocol for bicycle and treadmill exercise testing in patients with chronic cardiac failure. *European Heart Journal* 1992;**13**:1363-1367.

Rose, G., Barker, D.J.P. Epidemiology for the unititiated. (2nd edition) London: British Medical Journal.1982

Roul, G., Muolichon, M.E., Bareiss, P., et al. Exercise peak VO2 determination in chronic heart failure: is it still of value? *European Heart Journal* 1994;**15**:495-502.

Rouleau, J.L., de Champlain, J., Klein, M., et al. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. *J. Am. Coll. Cardiol.* 1993;**22**:390-398.

Sahn, D.J., De Maria, A., Kusslo, J., Weyman, A. The committee of M-Mode standardisation of the American Society of Echocardiography-results of a survey of echocardiographic methods. *Circulation* 1978;**58**:1072-1083.

Samani, N.J., Thompson, J.R., Otoole, L., et al. A metaanalysis of the association of the deletion allele of the angiotensin-converting enzyme gene with myocardial-infarction. *Circulation* 1996;**94**:708-712.

Sanderson, J.E., Young, R.P., Yu, C.M., et al. Lack of association between insertion/deletion polymorphism of the angiotensin-converting enzyme gene and end-stage heart failure due to ischemic or idiopathic dilated cardiomyopathy in the chinese. *Am. J. Cardiol* 1996;**77**:1008-1010.

Schieken, R., Clarke, W., Mahoney, L., Lauer, R. Measurement criteria for group echocardiographic studies. *American Journal of Epidemiology* 1979;**110**:(4):504-514.

Schiller, N.B., Acquatella, H., Ports, T.A., et al. Left ventricular volume from paired biplane two-dimensional echocardiography. *Circulation* 1979;**60**:(3):547-555.

Schocken, D.D., Arrieta, M.I., Leaverton, P.E., Ross, E.A. Prevalence and mortality rate of congestive heart failure in the United States. *J. Am. Coll. Cardiol.* 1992;**20**:301-306.

Schomish, M.C., Schluter, M.D., Paranandi, L., et al. Inotropic effects of angiotensin II on human cardiac muscle in vitro. *Circulation* 1990;**82**:1973-1984.

Schunkert, H., Hense, H.W., Holmer, S.R., et al. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left-ventricular hypertrophy. *N Engl J Med* 1994;**330**:1634-1638.

Schuster, H., Wienker, T., Stremmler, U., et al. An angionensin-converting enzyme gene variant is associated with acute myocardial infarction in women but not in men. *American Journal of Cardiology* 1995;**76**:601-603.

Senni, M., Rodeheffer, R.J., Evans, J.M., et al. Prognosis of congestive heart failure with normal systolic function in the community. *Heart Failure Update '97. Proc. of the Meeting* 1997;116-P455.

Singer, D.R.J., Missouris, C., Jeffery, S. Angiotensin-converting enzyme gene polymorphism. what to do about all the confusion? *Circulation* 1996;**94**:236-239.

Slinz, W., Schaper, J., Wiemer, G., et al. Ramipril prevents left ventricular hypertrophy with myocardial fibrosis without blood pressure reduction: a one year study in rata. *Br J Pharmacol* 1992;**107**:970-975.

Smith, W.C.S., Shwery, M.C., Tunstall-Pedoe, H., et al. Cardiovascular disease in Edinburgh and North Glasgow: a tale of two cities. *J Clin Epidemiol* 1990;**43**:637-643.

Soufer, R., Wohlgelertner, D., Vita, N.A., et al. Intact systolic left ventricular function in congestive heart failure. *Am. J. Cardiol.* 1985;**55**:1032-1036.

Stamm, R.B., Carabello, B.A., Mayers, D.L., Martin, R.P. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J* 1992;**104**:(1):136-144.

Starling, M.R., Crawford, M.H., Sorensen, S.G., et al. Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. *Circulation* 1981;**63**:(5):1075-1084.

Stevenson, R., Randjadayalan, K., Wilkinson, P., et al. Short and long term prognosis of acute myocardial infarction since the introduction of thrombolysis. *BMJ* 1993;**307**:349-353.

Stewart, A.L., Greenfield, S., Hays, R.D., et al. Functional status and well being of patients with chronic conditions. Results of the Medical Outcomes Study. *JAMA* 1989;**762**:907-913.

Sullivan, M.J., Higginbotham, M.B., Cobb, F.R. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988;**77**:552-559.

Sundsfjord, J.A., Thibault, G., Larochelle, P., Cantin, M. Identification and plasmsa concentrations of the N-terminal fragment of pro-atrial natriuretic factor in man. *J Clin Endocrinol Metab* 1988;**6**:605-610.

Sunman, W., Sever, P. Non-angiotensin effects of angiotensin-converting enzyme inhibitors. *Clinical Science* 1993;**85**:661-670.

Swedberg, K., IdanpaanHeikkila, U., Remes, J., et al. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429-1435.

Swets, J.A., Getty, D.J., Pickett, R.M., et al. Enhancing and evaluating diagnostic accuracy. *Med Decis Making* 1991;**11**:9-18.

Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the Diagnosis of Heart Failure. *European Heart Journal* 1995;**16**:741-751.

Teerlink, J.R., Goldhaber, S.Z., Pfeffer, M.A. An overview of contemporary etiologies of congestive heart failure. *Am Heart J* 1991;**121**:1852-1853.

The Multicentre Post Infarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;**309**:331-336.

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:(5):293-302.

The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N. Engl. J. Med.* 1992;**327**:685-691.

Townend, J., Littler, W. 1993; Angiotensin converting enzyme inhibitors in heart failure: how good are they? *British Heart Journal* **69**:373-375

Tsevat, J., Duke, D., Goldman, L., et al. Cost-effectiveness of captopril therapy after myocardial-infarction. *Journal of the American College of Cardiology* 1995;**26**:914-919.

Tunstall-Pedoe, H., Kuulasmaa, K., Amouyel, P., et al. Myocardial infarction and coronary deaths in the World Health Organisation MONICA Project. *Circulation* 1994;**90**:583-612.

Vasan, R.S., Larson, M.G., Benjamin, E.J., et al. Left ventricular dilation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997;**336**:1350-1355.

Vasan, R.S., Larson, M.G., Benjamin, E.J., et al. Left ventricular dilation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997;**336**:(19):1350-1355.

Wallen, T., Landahl, S., Hedner, T., et al. Brain natriuretic peptide predicts mortality in the elderly. *Heart* 1997;**77**:264-267.

Weber, K.T., Wilson, J.R., Janicki, J.S., Likoff, M.J. Exercise testing in the evaluation of the patient with chronic cardiac failure. *Am Rev. Respir. Dis.* 1984;**129**:S60-2.

Weber, K.T., Sun, Y., Katwa, L.C., et al. Connective-tissue and repair in the heart - potential regulatory mechanisms. *Annals Of The New York Academy Of Sciences* 1995;**752**:286-299.

Weber, K.T., Janicki, J.S. Cardiopulmonary exercise testing for the evaluation of chronic heart failure. *Am J Cardiol* 1985;**55**:22A-31A.

Wei, C.M., Heublein, D.M., Perrella, M.A., et al. Natriuretic peptide system in human heart failure. *Circulation* 1993;**88**:1004-1009.

Wheeldon, N.M., MacDonald, T.M., Flucker, C.J., et al. Echocardiography in chronic heart failure in the community [see comments]. *Q. J Med.* 1993;**86**:17-23.

Wheeldon, N.M., MacDonald, T.M., Flucker, C.J., et al. Echocardiography in chronic heart failure in the community. *Q. J Med.* 1993;**86**:17-23.

Wilson, J.M.G. The worth of screening. *Proc R Coll Physicians Edin* 991;**21**:288-310.

Wilson, J.M.G., Junger, G. Principles and practice of screening for disease. WHO. Geneva.1968.

Wilson, J.R., Fink, L., Maris, J., et al. Evaluation of energy metabolism in skeletal muscle of patients with heart failure with gated phosphorus-31 nuclear magnetic resonance. *Circulation* 1985;**71**:57-62.

Wong, M., Johnson, G., Shabetai, R., et al. Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure. Veterans Affairs cooperative studies V-HeFT I and II. V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**:VI65-70.

Yamamoto, K., Burnett JC Jr, Jougasaki, M., et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 1996;**28**:988-994.

Yasue, H., Yoshimura, M., Sumida, H., et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994;**90**:195-203.

Yoshimura, M., Yasue, H., Okumura, K., et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation* 1993;**87**:464-469.

Yusuf, S., Wittes, J., Friedman, L. Overview of results of randomised clinical trials in heart disease. Treatments following myocardial infarction. *JAMA* 1988;**260**:2088-2093.

Zelis, R., Longhurst, J., Capone, R.J., Mason, D.T. A comparison of regional blood flow and oxygen utilisation during dynamic forearm exercise in normal subjects and in patients with congestive cardiac failure. *Circulation* 1974;**50**:137-143.

Zelis, R., Musch, T.I., Sinoway, L.I. The maximal stress test: does it have any value in heart failure? *J. Am. Coll. Cardiol.* 1990;**15**:62-63.

Zhao, Y., Higashimori, K., Higaki, J., et al. Significance of the deletion polymorphism of the angiotensin converting enzyme gene as a risk factor for myocardial infarction. *Hypertens Res* 1994;**17**:55-57.

PUBLICATIONS ARISING FROM THIS THESIS

FULL PAPERS:

Symptomatic and Asymptomatic Left Ventricular Systolic Dysfunction in an Urban Population.
T A McDonagh, CE Morrison, H Tunstall -Pedoe, I Ford, JJV McMurray and HJ Dargie.
Lancet 1997;**350**:829-833.

Biochemical Detection of Left Ventricular Dysfunction.
TA McDonagh, SD Robb, CE Morrison, H Tunstall-Pedoe, I Ford, JJ McMurray and HJ Dargie.
Lancet. 1998;**351**:9-13.

Helicobacter pylori infection and coronary heart disease in the North Glasgow MONICA population.
TA McDonagh, M Woodward, CE Morrison, JJV McMurray, H Tunstall-Pedoe, GDO Lowe, KEL McColl, HJ Dargie.
Eur Heart J 1997;**18**:1257-1260.

FULL PAPERS SUBMITTED FOR PUBLICATION

Associations Between the ACE I/D Polymorphism, Coronary Heart Disease and Left Ventricular Dysfunction.
TA McDonagh, SD Robb, CE Morrison, H Tunstall-Pedoe, HJ Dargie, F Cambien, JJ McMurray.
Submitted to Circulation.

The Effect of Left Ventricular Systolic Dysfunction on Effort Capacity in an Urban Population.

TA McDonagh, BS Davison, J Byrne, AL Clark, JJ McMurray, HJ Dargie.

Submitted to JACC

Pulmonary Hypertension Detected by Echocardiography in an Urban Population

TA McDonagh, PJ Cowburn, E Rooney, JJ McMurray and HJ Dargie

Submitted to the Annals of Internal Medicine.

Left Ventricular Systolic Dysfunction According to Wall Motion Analysis in an Urban Population.

TA McDonagh, E Lundmark, JJ McMurray and HJ Dargie.

Submitted to the European Heart Journal

CHAPTER CONTRIBUTIONS TO BOOKS DRAWING ON THIS THESIS

What is Heart Failure ?

T A McDonagh and HJ Dargie.

The Management of Heart Failure in Primary Care.

Ed. HJ Dargie, P Poole-Wilson, J McMurray.

Blackwell Science. 1996

Exercise Testing in the Diagnosis and Assessment of Heart Failure.

T A McDonagh and HJ Dargie.

In Heart Failure: Scientific Principles and Clinical Practice.

Ed. PA Pool-Wilson, W Colucci, K Chaterjee, B Massie, A Coats.

Churchill Livingstone. 1997.

ABSTRACTS ARISING FROM THE THESIS:

Detection of left ventricular systolic dysfunction in the population using the natriuretic peptides

TA McDonagh, SD Robb, CE Morrison, H Tunstall-Pedoe, HJ Dargie.

J Am Coll Cardiol (1997. Suppl)

Left Ventricular Ejection Fraction: What is Abnormal?

TA McDonagh, SD Robb, CE Morrison, H Tunstall-Pedoe, JJ McMurray, HJ Dargie.

European Society of Cardiology 1996.

Natriuretic Peptides as Screening Tools for Left Ventricular Dysfunction

TA McDonagh, SD Robb, CE Morrison, JJ Morton, H Tunstall-Pedoe, JJ McMurray, HJ Dargie.

European Society of Cardiology 1996.

Determinants of global left ventricular systolic dysfunction in North Glasgow

TA McDonagh, CE Morrison, JJV McMurray, I Ford, H Tunstall-Pedoe, HJ Dargie.

Heart (Suppl 1) 1996;75;5 (266).

Global left ventricular systolic dysfunction in North Glasgow.

TA McDonagh, CE Morrison, A Lawrence, JJV McMurray, I Ford, H Tunstall-Pedoe, HJ Dargie.

J Am Coll Cardiol 1996 (Suppl)

Symptomatic and Asymptomatic Left Ventricular Dysfunction in North Glasgow.

TA McDonagh, CE Morrison, JJ McMurray, H Tunstall-Pedoe and HJ Dargie.

Eur. Heart. J (Suppl) 1995;16:498(2839).

The assessment of ST segment depression during exercise testing.
TA McDonagh, CE Morrison, JJ McMurray, H Tunstall-Pedoe and HJ Dargie.
Eur. Heart. J (Suppl) 1995;16: 228(1303).

Left ventricular dysfunction in the North Glasgow Monica Population.
TA McDonagh, CE Morrison, JJ McMurray, I Ford, H Tunstall-Pedoe, HJ Dargie.
Br. Heart Journal;1995 73 (5) Suppl.3: 111.

The prevalence of left ventricular dysfunction in North Glasgow.
TA McDonagh, CE Morrison, JJ McMurray, H Tunstall-Pedoe and HJ Dargie.
American Heart Association, Dallas, November 1994.
Circulation.(Suppl.) i-283;1521.

The effect of psychological depression on functional capacity.
T A McDonagh, BS Davison, J Norrie, CE Morrison, JJ McMurray, H Tunstall-Pedoe and HJ Dargie.
American Heart Association, Dallas, November 1994.
Circulation. (Suppl.) 1-162;869.

Psychological depression and exercise capacity.
TA McDonagh, BS Davison, CE Morrison, JJ McMurray, JD Norrie, H Tunstall-Pedoe and HJ Dargie.
World Congress of Cardiology,Berlin, September 1994.
European Heart Journal (Suppl.) 15; 3267.

The effect of psychological depression on functional capacity.
TA McDonagh, BS Davison, C Morrison, J McMurray, H Tunstall-Pedoe and HJ Dargie.
British Cardiac Society May 1994.
Br Heart Journal (Supp) May 1994;71:5(p32.No 103).

Screening with natriuretic peptides to detect a wall motion score index of ≤1.2
TA McDonagh, CE Morrison, JJ McMurray, HJ Dargie
Heart Failure Update. Cologne 1997
Published in Proc of the Meeting

Detection of left ventricular dysfunction in an urban population using a wall motion score index.
TA McDonagh, CE Morrison, JJ McMurray, HJ Dargie
Heart Failure Update. Cologne 1997
Published in Proc of the Meeting

Population screening with natriuretic peptides to detect a wall motion score index of ≤1.2
TA McDonagh, CE Morrison, H Tunstall-Pedoe, JJ McMurray, HJ Dargie.
Heart 1997 Suppl.